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*THE GROWTH HORMONE

REPORT OF A CASE OF JUVENILE HYPOPITUITARISM TREATED WITH EVANS' GROWTH HORMONE

WILLIAM ENGELBACH
NEW YORK

Pituitary disorder as a clinical entity has rarely been identified in the preadolescent periods. With the exception of the rare occurrence of pituitary tumor, a perusal of the literature does not reveal a description of pituitary disorder during the early years of life. Notwithstanding medical opinion concerning its rarity, disorder of the hypophysis unassociated with pituitary tumor is prevalent in infancy and juvenility. The apparent infrequency of both deficiency and hyperactivity of the anteropituitary in the preadolescent years is due to the lack of recognition and interpretation of the objective hormonic signs of these disorders. It is well known that the growth hormone orginating from the eosinophilic cells of this lobe is actively operative from birth and during a number of months of prenatal life. Knowing that somatic growth is largely dependent upon the hormone derived from these pituitary cells, it must be supplied in very large amounts during infancy. If the growth hormone is supplied in normal amount in the first three years, the bodily development obtained equals one-half the total of the full-grown adult. Any reduction or excess of this hormone during the very rapid development of the infant necessarily results in an arrested or an accelerated growth. Since this fact has been known, eight cases of pure infantile pituitarisms uncomplicated by thyroid disorder or non-endocrine disease have been collected. Five of these are anterior lobe insufficiencies, one, suspected hyperactive, and two are probably adiposogenital pituitarisms. Of the anterior lobe disorders, one was diagnosed at two years of age; one, three years; one, three years and eleven months; one, four years; and two, five years. The adiposogenitalisms were respectively two years and eleven months and three years and eleven months. These have all been discovered in the last year and one-half, during which time much information has developed relative to the isolation of the "*growth hormone*" from this lobe. The application of the

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anterior lobe function to somatic growth, measured by the annual increment of anatomic stature, would undoubtedly flood the literature with many more case reports of this entity as anterior lobe insufficiency resulting in an infantile microsomatic individual contrasts very sharply with the overgrowth and macrosomatic effects produced by the early hyperactivity of the anteropituitary.

Following an original plan of classification, the pituitarisms of infancy are grouped as follows, first upon activity and second upon their lobar involvement:

Infantile Pituitarism

1. Anterior Lobe
   a. Hypopituitarism
   b. Hyperpituitarism
2. Adiposogenital Pituitarism
3. Pituitary Tumor

The infantile pituitarisms are similar to the thyroidisms of infancy in so far as the majority are hypoactive. With the exception of the less frequent hyperpituitarisms all disorders of this gland, including the occasional pituitary tumor of infancy, are hypopituitarisms, and of this activity there are comparatively few adiposogenital involvements. Their incidence in infancy differs from that of the juvenile and adolescent ages, which present a gradually increased percentage of adiposogenitalisms. Owing to the fact that at this period the sex hormones are not active, genital hypoplasia, if it is present, deviates from the normal so slightly as not to be appreciable. Consequently, the entire clinical picture due to lack or excess of the growth hormone is that of abnormal somatic under- or over-development. Reduction of the hormone at this age produces the opposite clinical effects of its overproduction of later epochs resulting in gigantism or acromegaly. Pituitary tumors of the preadolescent ages are usually either chiasmal gliomas or craniopharyngiomas of suprasellar origin, and consequently produce only secondary pressure effects upon the intrasellar anterior lobe. Adiposogenital pituitarism having evidence of disturbance of the sex hormones without growth hormone disorder of the anteropituitary is not included in this discussion.

SYNONYMS AND DEFINITIONS

Synonymous terms are infantile pituitarism, infantile hypopituitarism, anterior lobe deficiency, infantilism, Lorain-Levi disorder, infantile pituitary tumor. We are indebted to the French School, followers of Lorain and Levi, for the first descriptions of hypoactivity of the hypophysis. In 1871 Lorain first described a case of infantilism at the age of twelve. He characterized as infantilism an arrest of development, which affected the mass of the individual rather than any special organ, causing disability, delicacy, and smallness of the body associated with a genital dystrophy. He

noted the similarity of such an individual to one having tuberculosis or the cardiopathies developing during the preadolescent age. In 1908 Etteo Levi described a typical case of infantilism, associated with an enlargement of the sella, similar to that previously described by Lorain, in a girl twenty years and six months old who was four feet and four inches in height. This patient was a weak, delicate, undersized individual with the absence of primary and secondary sex characters and a bodily proportion of an infant. Her epiphyses had failed to unite, and the sella was enlarged and deformed, probably from pituitary tumor. There was absence of adiposity, to which attention had been directed some eight years previously by Fröhlich in the description of his adiposogenital dystrophy.

CYTOLOGY AND BIOCHEMISTRY

The pathology of the anterior lobe of the pituitary gland in these cases of aneoplastic infantile pituitarism has not been investigated. Hence, it must be hypothecated largely from the cytology of anterior lobe hypo- and hyper-plasias occurring in later life. Positive knowledge concerning the production of growth hormones by the eosinophilic cells of the anterior lobe, and the excessive amount of these hormones found in the blood and urine in the pituitary adenomas resulting in overgrowth in the adult, would permit conclusions referring the infantile *hyperpituitarisms* to hyperplasia of these cells. Conversely, it is taken for granted that the undergrowth of *hypopituitarism* is due to the reduction of this hormone caused by hypoplasia of the eosinophilic cells. The genital hormones derived from the basophilic and chromophobic cells are not produced until the latter years of juvenility, and consequently do not participate in this endocrinism. For this reason the clinical picture is one related to the annual increment in size and form of all the organs of the body, of which the statural characteristics are the most outspoken.

On this basis the biochemistry is that of a deficiency in the hypopituitarism and excess in the hyperpituitarism of the growth hormone of the anterior lobe of the hypophysis. These infantile anterior lobe disorders are identical with those producing complete hypopituitarism of the Lorain-Levi type or hyperpituitarism resulting in gigantism of the juvenile and adolescent periods. Delayed maturity and underdevelopment of the genitals in these insufficiencies does not appear until the latter years of juvenility or early adolescence.

Consequently, there is no evidence of eosinophilic disorder of the anterior lobe. The lack of genital development, however, would indicate disorder of the chromophobic cells. Whether the adiposity of this variety of pituitarism is related to these cells of the anterior lobe, the posterior lobe, or the cerebral centers, is yet debatable.

ETIOLOGY

Deficiency of the anterior lobe during the early years of infancy must be inherited. Proof of this depends upon a familial history of pituitarism,

or the lack of pituitary response during gravidity, at which time the embryonic hypophysis is being evolved. The apparent rarity of these infantile cases does not permit other deduction concerning their etiology. The cases reported here indicate that they are not acquired. The earlier in life their diagnosis becomes possible, the more definite would become their hereditary etiology. The diagnosis of pituitary activity at birth or during the first year, before extrinsic causation could become operative, would support such conclusions. The earliest case in this series is one of two years of age. Of the eight cases, five were recognized before the age of four. None of these cases had a history of exogenous causation which might be held responsible for their condition. On the other hand, of the eight cases, six had positive history of either parental or familial endocrinopathies. In the two others the family history was unobtainable. The endogenous family history of the six consisted of positive pituitary or thyropituitary disorders in four and diabetes in two. Many mild inactivities of the hypophysis undoubtedly occur during infancy, evidencing such minor deviations in growth increment as to make their recognition difficult. These partial or potential pituitarisms increase the susceptibility to the infantile intoxications and infections. Consequently, they are easily activated by these exciting causes, which apparently fixes their onset a number of years after birth. With regard to sex and age, five of these cases were females and three males. Two occurred in the second year, three in the third year, one in the fourth year, and two in the fifth year.

Of these eight infantile pituitarisms six were diagnosed anterior lobe disorders; one, a hyperactivity; and five, hypoactivities. The remaining two cases were diagnosed adiposogenital pituitarisms. It is emphasized that other factors, endogenous and exogenous, have a considerable influence upon the somatic growth and the development of the osseous and genital systems. Consequently, it must not even be taken for granted that all types of infantilism are due to endocrine disorder. Pituitary infantilism is herein defined as a general arrest of growth and development of all organs and systems of the body due to inactivity of both the growth and genital hormones of the anterior lobe of the hypophysis. This early form of pituitary inactivity does not include such dwarfs as described by Paltauf or the groups of Lilliputians. Neither does it embrace those ateliosic or progeric forms of Hastings Gilford designated "continuous youth" and "premature old age." Some of the above infantilisms may be due to a partial insufficiency of the anterior lobe involving its eosinophilic cells without affecting its basophilic or chromophobic elements. Such involvement would result in retarding somatic growth without arresting the maturity, development and function of the genital system. All primary non-endocrine causation must be excluded in these cases as well as the other endocrinisms. Consequently, Herter's type of infantilism attributed to chronic intestinal infection and the many types given by Peretz, due to deficiency of proteins and vitamins are excluded. While

these non-endocrine causes may, through their effect upon anterior lobe function, influence development, such possibility would exclude them from being primary anterior lobe insufficiencies. The deficiency of both growth and genital pituitary hormones produces an arrest and underdevelopment of the entire body with a failure of the maturity of the primary and secondary sex characteristics at adolescence. Many of the dwarfs, consequently, would not belong to this group owing to the fact that they have fairly normal sexual development and function after the age of adolescence. They differ from pituitary infantilism before adolescence by their lack of retention of the infantile stature of height-weight and proportions or upon the presence of other causes for dwarfism, such as retarded osseous development present in hypothyroidism. The different types of dwarfism (Lilliputians, Paltauf's type, rachitic dwarfs, cretinisms, chondrodystrophy, and Mongolianism) usually have sufficient characteristic signs of their anomaly. While the genitalia in most of these dwarfs is underdeveloped, many of them have the normal function of these organs. Their epiphyses appear at the normal age, and unite earlier than those of pituitary infantilism. Rachitic dwarfs have typical signs of rickets, such as rosary and osseous signs described in the differential diagnosis under congenital hypothyroidism. None of these groups of cases has the perfect combination of arrested skeletal growth with late closure of the epiphyseal centers, associated with a complete lack of development and insufficiency of the function of the gonads following the age of adolescence. Achondroplasia differs by having an unusually long torso as compared with the short extremities, fingers of the same length, well developed genitals, and epiphyses which appear and unite at the normal age. The morons or mongols are easily separated from this type of hypopituitarism by the marked defect in the mentality and the absence of postadolescent hypoplasia of the gonads in the presence of normal time of epiphyseal closure.

SYMPTOMATOLOGY

The symptomatology of these infantile pituitarisms depends almost entirely upon the sufficiency of the growth hormone. If this growth hormone is deficient, there will be a retardation or arrest of the physical development during infancy. On the other hand, if it is excessive there will be an overdevelopment of the entire body and its organs. The clinical expression of a marked under- or over-growth during infancy is the most important index of the activity of the anterior lobe of this gland. Upon its function at this time is dependent the future development of all the bodily organs. For this reason the physical development during infancy should be carefully supervised and compared with the normal for the age.

Table I includes the normal variation of normal measurements in each sex to the age of twenty years. Minimal-maximal measurements for each sex are given for each month during the first year, every third month of the second and third years, and for six-months intervals after the third year.

TABLE I.—NORMAL MEASUREMENTS IN RELATION TO AGE.

AGE	Height (inches) M Min.	M Max.	F Min.	F Max.	Weight (pounds) M Min.	M Max.	F Min.	F Max.	Span (inches) M Min.	M Max.	F Min.	F Max.	Upper Measurement (inches) M Min.	M Max.	F Min.	F Max.	Lower Measurement (inches) M Min.	M Max.	F Min.	F Max.	Circumference Measurements (inches) Head M	Head F	Chest M	Chest F	Waist M	Waist F
Birth	19.3	21.1	19.0	20.8	6.2	8.6	6.4	8.6	18.1	20.1	18.1	19.9	12.1	13.1	12.1	13.1	6.9	7.9	6.9	7.9	13.9	13.6	13.8	13.6	13.4	13.2
1 Mo.	20.9	22.9	20.5	22.5	9.0	11.8	8.4	11.0	20.1	22.1	19.5	21.5	13.3	14.3	13.0	14.0	7.7	8.7	7.5	8.5	15.2	14.9	14.3	14.1	13.8	13.6
2 Mos.	22.1	24.1	21.7	23.7	10.4	13.6	9.8	12.6	21.0	23.0	20.4	22.4	13.9	14.9	13.6	14.6	8.1	9.1	7.9	8.9	16.0	15.7	15.6	15.3	15.2	15.0
3 "	23.1	25.1	22.7	24.7	11.9	15.3	11.2	14.2	22.0	24.0	21.4	23.4	14.5	15.5	14.1	15.1	8.5	9.5	8.4	9.4	16.6	16.3	16.4	16.0	16.0	15.7
4 "	24.0	26.0	23.6	25.6	13.2	16.8	12.4	15.8	22.9	25.1	22.3	24.3	15.0	16.0	14.7	15.7	9.0	10.0	8.8	9.8	17.0	16.7	16.9	16.5	16.5	16.2
5 "	24.7	26.7	24.3	26.3	13.9	17.7	13.7	17.3	23.3	25.5	23.3	25.3	15.3	16.3	15.2	16.2	9.2	10.2	9.3	10.3	17.4	17.1	17.2	16.8	16.8	16.5
6 "	25.4	27.4	25.0	27.0	15.2	19.4	14.3	18.1	24.3	26.5	23.6	25.8	15.9	16.9	15.5	16.5	9.6	10.6	9.5	10.5	17.7	17.3	17.5	17.0	17.1	16.8
7 "	26.1	28.1	25.6	27.6	15.9	20.1	14.9	18.9	24.8	27.0	24.3	26.3	16.1	17.1	15.8	16.8	9.9	10.9	9.7	10.7	17.9	17.5	17.7	17.2	17.3	17.0
8 "	26.6	28.6	26.1	28.1	16.5	20.9	15.6	19.6	25.3	27.5	24.8	26.8	16.3	17.5	16.0	17.0	10.0	11.2	10.0	11.0	18.1	17.7	17.9	17.4	17.5	17.2
9 "	27.1	29.1	26.6	28.6	17.1	21.7	16.1	20.3	25.8	28.0	25.2	27.2	16.5	17.7	16.3	17.3	10.3	11.5	10.2	11.2	18.2	17.8	18.0	17.6	17.6	17.3
10 "	27.6	29.6	27.1	29.1	17.6	22.4	16.6	21.0	26.2	28.4	25.7	27.7	16.8	18.0	16.4	17.6	10.5	11.7	10.4	11.6	18.4	18.0	18.2	17.9	17.7	17.4
11 "	28.1	30.1	27.6	29.6	18.3	23.1	17.3	21.7	26.7	28.9	26.1	28.3	17.0	18.2	16.7	17.9	10.8	12.0	10.6	11.8	18.5	18.1	18.3	17.9	17.8	17.5
12 "	28.4	30.6	28.0	30.0	18.9	23.9	17.8	22.4	27.2	29.4	26.6	28.8	17.3	18.5	16.9	18.1	11.0	12.2	10.9	12.1	18.6	18.2	18.5	18.1	17.9	17.6
15 "	29.6	31.8	29.1	31.3	21.0	25.8	18.9	23.7	28.2	30.4	27.6	29.8	17.8	19.0	17.4	18.6	11.5	12.7	11.4	12.6	18.9	18.5	18.8	18.4	18.2	17.9
18 "	30.8	33.0	30.3	32.5	21.9	27.3	20.6	25.8	29.6	32.0	29.0	31.2	18.6	19.8	18.1	19.3	12.2	13.4	12.2	13.4	19.1	18.7	19.1	18.7	18.5	18.2
21 "	31.7	34.1	31.3	33.5	23.1	28.7	21.7	27.1	30.6	33.0	29.9	32.3	18.9	20.3	18.6	19.8	12.7	14.1	12.7	13.9	19.3	18.9	19.4	19.0	18.7	18.4
24 "	32.7	35.1	32.2	34.6	24.3	30.1	22.9	28.5	31.5	33.9	30.9	33.3	19.4	20.8	18.9	20.3	13.2	14.6	13.2	14.6	19.4	19.0	19.7	19.2	18.9	18.5
30 "	34.5	36.9	33.9	36.3	26.1	32.3	24.7	30.7	32.9	35.5	32.4	34.8	20.0	21.4	19.6	21.0	14.1	15.5	14.0	15.4	19.6	19.2	20.2	19.6	19.2	18.9
36 "	36.0	38.6	35.4	38.0	28.7	35.3	26.6	33.0	34.8	37.6	33.8	36.4	20.7	22.3	20.0	21.6	15.2	16.8	14.9	16.5	19.8	19.4	20.6	20.0	19.5	19.1
42 "	37.4	40.2	36.9	39.5	30.5	37.5	28.6	35.2	36.3	39.1	35.2	38.0	21.3	22.9	20.6	22.2	16.1	17.7	15.8	17.4	20.0	19.6	21.0	20.4	19.8	19.3
48 "	38.8	41.6	38.3	40.9	31.8	39.2	30.5	37.5	37.3	40.3	36.7	39.5	21.6	23.2	21.2	22.8	16.9	18.4	16.7	18.3	20.1	19.7	21.4	20.7	20.0	19.5
54 "	40.1	42.9	39.5	42.3	33.2	41.6	32.5	39.9	38.8	41.8	38.2	41.2	22.0	23.8	21.5	23.3	17.7	19.5	17.7	19.5	20.3	19.9	21.7	21.0	20.2	19.7
60 "	41.2	44.2	40.7	43.7	35.1	43.5	33.9	41.6	39.8	43.0	39.2	42.2	22.4	24.2	21.9	23.7	18.3	20.1	18.3	20.1	20.4	20.0	22.1	21.4	20.4	19.9
5½ Yrs.	42.4	45.4	41.9	44.9	37.4	46.4	35.9	44.5	41.3	44.5	40.7	43.9	22.7	24.7	22.4	24.2	19.3	21.3	19.3	21.1	20.4	20.1	22.4	21.7	20.6	20.0
6 "	43.5	46.5	43.1	46.1	39.2	48.6	37.5	46.5	42.4	45.6	41.7	44.9	23.0	25.0	22.6	24.6	20.0	22.0	19.9	21.9	20.5	20.1	22.7	22.0	20.9	20.2
6½ "	44.5	47.7	44.2	47.2	41.0	50.8	39.2	48.8	43.4	46.8	42.8	46.0	23.3	25.3	23.0	25.0	20.7	22.7	20.5	22.5	20.5	20.2	23.0	22.3	21.1	20.4

	Height (inches)				Weight (pounds)				Span (inches)				Upper Measurement (inches)				Lower Measurement (inches)				Circumferences Measurements (inches)					
	M		F		M		F		M		F		M		F		M		F		Head		Chest		Waist	
AGE	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	M	F	M	F	M	F
7 "	45.6	48.8	45.2	48.4	48.0	53.2	42.1	52.3	44.5	47.9	44.3	47.7	23.5	25.7	23.4	25.4	21.3	23.5	21.6	23.6	20.6	20.3	23.3	22.7	21.3	20.5
7½ "	46.5	49.8	46.3	49.5	48.0	55.8	44.1	54.9	45.8	49.1	45.4	48.8	23.8	26.0	23.7	25.9	22.0	24.2	22.1	24.3	20.7	20.3	23.7	23.0	21.8	20.7
8 "	47.5	50.9	47.2	50.6	47.2	59.4	46.4	57.6	46.8	50.4	46.5	49.9	24.1	26.3	24.0	26.2	22.7	24.9	22.8	25.0	20.7	20.4	24.0	23.4	21.8	20.8
8½ "	48.5	51.9	48.2	51.6	49.8	61.3	48.6	60.6	48.0	51.6	47.8	51.1	24.5	26.7	24.4	26.6	23.3	25.5	23.4	25.6	20.8	20.5	24.3	23.8	22.0	21.0
9 "	49.5	52.9	49.2	52.6	51.6	64.4	51.0	63.8	49.1	52.9	48.6	52.2	24.7	27.1	24.7	26.9	23.9	26.3	24.1	26.3	20.9	20.5	24.6	24.2	22.3	21.2
9½ "	50.4	54.0	50.1	53.7	54.2	67.8	53.6	67.2	50.3	54.1	49.6	53.4	25.1	27.5	25.0	27.4	24.5	26.9	24.6	27.0	20.9	20.6	25.0	24.6	22.6	21.5
10 "	51.4	55.0	51.2	54.8	57.0	71.6	56.2	71.0	51.4	55.4	50.7	54.5	25.5	27.9	25.5	27.9	25.1	27.5	25.1	27.5	21.0	20.7	25.3	25.0	22.8	21.8
10½ "	52.4	56.0	52.3	55.9	59.9	75.5	59.3	75.1	52.5	56.5	51.7	55.7	25.7	28.3	25.8	28.4	25.7	28.3	25.6	28.2	21.0	20.8	25.7	25.5	23.0	22.1
11 "	53.3	57.1	53.4	57.2	63.0	79.4	63.7	81.1	53.5	57.7	53.3	57.3	26.1	28.7	26.5	29.1	26.3	28.9	26.4	29.0	21.1	20.9	26.1	26.1	23.3	22.4
11½ "	54.3	58.1	54.6	58.4	66.2	83.2	66.9	85.5	54.6	58.8	54.2	58.4	26.5	29.1	26.9	29.5	26.9	29.5	27.0	29.6	21.2	20.9	26.6	26.6	23.6	22.8
12 "	55.2	59.0	55.6	59.6	69.4	87.2	70.7	90.5	55.8	60.0	55.4	59.6	27.0	29.6	27.4	30.0	27.4	30.0	27.5	30.1	21.2	21.0	27.0	27.1	23.9	23.2
12½ "	56.0	60.0	56.7	60.7	72.7	91.8	74.8	95.7	56.9	61.3	56.4	60.6	27.3	30.1	27.7	30.5	27.9	30.7	28.0	30.8	21.3	21.1	27.5	27.6	24.2	23.6
13 "	56.9	60.9	57.7	61.7	75.9	95.7	78.7	101.3	58.0	62.4	57.6	61.8	27.7	30.5	28.2	31.0	28.5	31.3	28.5	31.3	21.4	21.2	28.0	28.1	24.6	23.9
13½ "	57.8	61.8	58.5	62.7	79.3	100.3	83.6	107.2	59.0	63.6	58.6	63.0	28.2	31.0	28.8	31.6	29.0	31.9	28.9	31.9	21.5	21.3	28.6	28.5	25.0	24.2
14 "	58.6	62.8	59.3	63.6	81.1	102.9	89.3	113.5	59.6	64.2	59.1	63.5	28.4	31.2	29.2	32.0	29.3	32.1	29.6	32.3	21.6	21.4	29.1	28.9	25.4	24.5
14½ "	59.5	63.7	59.9	64.1	85.0	108.0	92.4	116.6	60.7	65.3	60.2	64.6	28.8	31.8	29.6	32.3	29.7	32.7	29.7	32.5	21.7	21.5	29.7	29.3	25.9	24.7
15 "	60.3	64.5	60.4	64.6	89.4	113.4	95.7	119.7	61.7	66.5	60.7	65.3	29.3	32.3	29.8	32.6	30.2	33.2	29.9	32.7	21.8	21.6	30.3	29.6	26.4	24.8
15½ "	61.1	65.3	60.8	65.0	91.6	116.2	99.0	122.8	62.3	67.1	61.3	65.9	29.5	32.5	30.1	32.9	30.5	33.5	30.1	32.9	21.9	21.7	31.0	29.9	26.8	25.0
16 "	61.9	66.2	61.1	65.3	96.0	122.0	99.0	122.8	63.4	68.2	61.3	65.9	30.0	33.0	30.1	32.9	31.0	34.0	30.1	32.9	22.0	21.7	31.7	30.1	27.2	25.1
16½ "	62.5	66.9	61.4	65.6	98.4	125.0	102.5	125.9	63.9	68.9	61.9	66.5	30.3	33.3	30.4	33.2	31.2	34.2	30.3	33.1	22.1	21.8	32.3	30.3	27.5	25.2
17 "	63.2	67.6	61.6	65.8	103.8	131.6	102.5	125.9	65.0	70.0	61.9	66.5	30.7	33.7	30.4	33.2	31.8	34.8	30.3	33.1	22.2	21.8	32.9	30.5	27.8	25.3
17½ "	63.8	68.2	61.8	66.0	106.8	136.2	106.1	128.9	65.6	70.6	62.5	67.1	31.0	34.0	30.7	33.5	32.0	35.0	30.5	33.5	22.3	21.8	33.3	30.7	28.0	25.4
18 "	64.4	68.8	61.9	66.1	109.8	139.0	106.1	128.9	66.1	71.1	62.5	67.1	31.3	34.3	"	"	32.2	35.2	"	"	22.4	21.9	33.7	30.8	28.2	25.5
18½ "	64.9	69.3	"	"	113.3	142.3	"	"	66.6	71.8	"	"	31.6	34.6	"	"	32.4	35.4	"	"	22.4	21.9	34.1	30.8	28.4	25.5
19 "	65.3	69.7	"	"	117.2	145.6	"	"	67.2	72.4	"	"	31.9	34.9	"	"	32.6	35.6	"	"	22.5	21.9	34.4	30.9	28.5	25.6
19½ "	65.6	70.0	"	"	121.5	148.5	"	"	67.8	73.0	"	"	32.1	35.3	"	"	32.7	35.9	"	"	22.5	21.9	34.6	30.9	28.6	25.6
20 "	65.8	70.2	"	"	121.5	148.5	"	"	67.8	73.0	"	"	32.1	35.3	"	"	32.7	35.9	"	"	22.5	21.9	34.7	31.0	28.7	25.7

Measurements made of a given child at each month and year as compared with above standards should serve as an index of the normal growth progress during these five years of infancy and juvenility. Any deviation below the minimum or above the maximum would indicate an insufficiency or oversupply of the growth hormone, *provided all other causes for abnormal growth can be excluded.*

CASE REPORTS

Two illustrative cases of preadolescent pituitary disorder will be reported. The first case is a classical one of infantile pituitarism in a patient three years, eleven and one-half months old at the first observation. Case 2 is an example of a complete insufficiency of the anterior lobe of the juvenile period first diagnosed at nine years and six months. The second patient is of particular interest on account of the fact that she was the first human to receive treatment consisting of Evans' growth hormone, to which she reacted remarkably.

Case 1. Infantile pituitarism, anterior lobe insufficiency.

History.—Gen. No. 6030. Miss B. L. B., 3 years and 11½ months, was referred by Dr. Paul F. Guernsey, Los Angeles, 8-27-29.

The patient is one of two children. She has one brother, seven years old, who is normal for age. She was a full-term baby, and her weight at birth was 5 lbs. 12 oz. The first tooth appeared at eleven months; she walked and talked at fifteen and one-half months. She was breast-fed for three and one-half months. Her first year was free from gastrointestinal upset and other illnesses. Definite retardation in her weight and height was noted during her first year. At the age of three years eleven and one-half months she weighed about the same as her brother at one year. Her mentality was normal. Her delivery was instrumental with a low forceps operation. The pregnancy was normal, during which time her mother gained 15 lbs. in weight.

The patient had had chicken pox, laryngitis and a number of attacks of mild bronchitis, without effect upon growth progression. She always had had a small appetite. The diet had been varied and well-balanced. An enlarged lymph node had been noted in the posterior cervical fossa. Ear infection and tonsillitis had not occurred.

The mother weighed 133 lbs., and her height was 5 ft. 2¼ in. Her weight at birth was 7½ lbs. and she was considered a fat baby. From the age of one year until maturity at twelve, the mother was not overweight and was of average height. Her menses were normal and she had no thyroid enlargement during adolescence or pregnancy. During first pregnancy she evidently had normal endocrine response. The total gain in weight during this gravidity was 17½ lbs., and she had no marked puffiness, alabaster color nor toxic symptoms of pregnancy. Her first baby weighed 6¾ lbs. at birth, 28 lbs. at one year, had normal dentition, walked and talked at the normal time. The father was 5 ft. 10 in. in height. His weight varied from 160 to 180 lbs. during the last few years. The maternal grandmother was 4 ft. 11 in. in height and was not obese. On the maternal side, there were a number of male relatives who were over 6 ft. in height. The paternal aunt was of the adoposo-genital pituitarism type with girdle obesity and long intervals of amenorrhea. (Note the pituitarism in almost every relative.)

Examination.—General:	*Actual*	*Normal Variations Absolute*
Weight	28.0 lb.	30.5-37.5 lb.
Height	37.0 in.	38.3-40.9 in.
Span	34.0 "	26.7-30.5 "
Upper measurement	20.0 "	21.2-22.8 "
Lower measurement	17.0 "	16.7-18.3 "
Upper to lower	20.0-17.0 "	13.6-15.0 "
Circumference of head	19.0 "	19.7 in. (opt.)
Circumference of chest	19.0 "	20.7 " (")
Circumference of abdomen	17.0 "	19.5 " (")

The measurements were below the minimum for age. The patient was very alert and responsive mentally. No abnormal skin, hair or mucous membrane changes were present. The musculature was of only fair tonicity, and slightly flaccid.

The head was small, but in proportion to the size of the body. The features were well placed, and the nose was not retrousse. The eyes were free from internal strabismus. The pupils were equal and regular and reacted to light and accommodation. No thyroid eye signs were present. There was no disturbance of hearing. The nose was normal. There was separation of the upper incisors with some spacing of canines and upper premolars. The tongue was not enlarged. The posterior cervical glands were bilaterally enlarged. The left submaxillary and submental were not palpable. The inguinal glands, both vertical and oblique, were palpable but the epitrochlear were not involved. The thyroid gland was not palpable. The thymus was not enlarged on percussion. The lungs were normal. There was no physical evidence of tracheobronchial involvement. The D'Espine sign was negative. The apex beat was not wide nor heaving and no thrill nor bruit was present. The sound at the apex and base were slow, pure, regular, and there were no murmurs nor accentuated second sounds on auscultation. No pot-belly, protrusion nor umbilical hernia was present. The spleen was not enlarged. The right kidney was palpable but not enlarged. The external genitalia were normal. The extremities were normal. Full extension of the thigh on the leg permitted complete hyperextension. The joints were frail and loose. The reflexes were normal and equal.

Laboratory examination.—Urine and blood analyses were normal. A roentgenographic lateral view of the head showed the sella to be normal in size, clear-cut, and well defined. Suture markings were ununited. Convolution indentations were present on the internal plate, particularly in the posterior and anterior fossa. The sinuses were normal in size. Mastoid cells were well aerated. Orthodontial markings were normal for age. There was advanced osseous development of almost a year. In the hand six carpal bones were present (capitate, hamate, triangularis, lunate, trapezium, and scaphoid). The normal number for this age is four carpals (capitate, hamate, triangularis, and lunate). The epiphyses for the metacarpals and phalanges were normal in size. The osseous development of the elbow was normal, and the capitellum of the humerus well developed. The proximal epiphysis of the radius was absent. There was slightly advanced ossification of the knee. From a lateral view the patella center was small but distinctly visible. The proximal epiphysis of the fibula was larger than normal for the age. The proximal epiphyses of the tibit and distal femur were normally developed. The osseous development of the ankle was normal. The distal epiphyses of the tibia and fibula were large and well formed. Seven tarsal bones were present (talus, cuboid, calcaneus, external cuneiform, middle cuneiform, and scaphoid). There was no enlargement of the thymus shadow. The heart was normal for the size of the chest but not for the age. Thyroid shadow was absent. Epiphyses of the head of the humerus and greater tuberosity were normal in size and ununited. (They normally unite at six years.) The osseous development of the hip was normal. The greater trochanter was well developed. Distal epiphyses of pubes and ilium were widely separated. (They normally unite at seven years). The proximal epiphyses of ilium, pubes, ischium are ununited. The head of the femur was large.

DISCUSSION

The symptomatology of the anterior lobe deficiencies during infancy refers almost entirely to marked retardation or arrest of the growth of the body and its organs. Somatic development is very easily estimated by comparison with the normals for the monthly age. The normality of the size of the various organs of the body, however, is more difficult to determine owing to the fact that there are, so far, no standards established for their size or weight during infancy. One exception to this rule would be the size and contents of the stomach during the first year of life, at which time gradual increase in capacity has been determined. This could be estimated by the fluoroscopic examination by which its size and capacity could be easily measured. Experiments have shown that hypophysec-

tomized puppies, which have lived more than a year, have a relative decrease of one-third of the size of all their organs as compared to their litter-mate controls.

Reichert has demonstrated both the withdrawal and the replacement effects of the growth hormone of the anterior lobe of the hypophysis. (1) By total hypophysectomy he arrested the growth and development of a dog for over a year. Then (2) by giving injections of extracts of the hypophysis (Evans' preparation) he succeeded in producing a greater growth and weight in this dog than its control litter-mate. Similar growth effects in infants are obtainable by replacement of antuitrin hypodermatically.

In these cases, then, the retardation of general body growth and weight is the most important clinical manifestation. Reduction in the annual or monthly increment or a retardation or arrest at any period of infancy *without extrinsic cause* should make one suspect an insufficiency of the anterior lobe of the hypophysis. Accurate determination of this is made by comparing actual measurements and weight of the patient with the normals for the age. There are exceptionally few other general hormonic signs in evidence at this age. In addition to these positive hormonic signs of anterior lobe pituitarism, there is usually some orthodontial evidence of this disorder. Separation of the teeth even at an early age is always suggestive of pituitarism. In an anterior lobe insufficiency, in addition to the unusual spacing of the upper front deciduous set, the teeth are usually miniature, comparable to the diminution of the body as a whole. There is no evidence of deficiency of the genital hormones until the late juvenile age. If the thyroid has been properly developed in the embryo, the genital organs have been well differentiated and the testicles have undergone normal descent. For this reason, in pituitarism, cryptorchism or genital anomalies are rarely present at birth or during infancy. That this normal tissue differentiation has taken place is demonstrated by roentgenographic studies of the osseous centers, which are found normal or advanced in time of appearance and development. This contrasts decidedly with hypothyroidism, in which there is a small stature due to lack of embryonic differentiation as is shown in the retarted osseous centers, internal strabismus, late eruption of the teeth, and undescended testicles.

Case 2. Juvenile hypopituitarism reacting to Evans' growth hormone.

History.—Gen. No. 6108. Miss J. M., 9 years and 6 months, was referred by Dr. A. Alsup, Honolulu, T. H., 9-16-30.

The chief presenting complaints were: (1) Physical underdevelopment, and (2) diminished appetite. These conditions had been present from birth.

The weight at birth was slightly under 7 lbs. Her delivery was normal. No symptoms were present immediately after delivery. During the first six months of life there was a rapid gain in weight. The patient was breast-fed. There were no gastrointestinal anomalies during the first year and no physical anomalies with the exception of overweight. The first tooth did not erupt until the age of one year. She was able to sit alone at six months. Her walking was delayed until four years. She talked well before one year. Her overweight persisted until the age of two. She failed to grow in height, however, from the first year. Growth was very slight up to the age of six, when the parents became apprehensive concerning development. At six she was 36 inches in height. During the last three years she had not grown in height.

With the exception of whooping cough, she has had practically no previous illnesses. It has been difficult to get her to take food. She eats a very small amount, estimated at less than one-third the intake of a normal child of her age. She has been inclined to sleep soundly throughout the night and three to four hours during the day but is easily aroused. Her mentality has been especially good throughout her life. She entered kindergarten at seven, not being permitted to enter sooner because of diminutive size. Her progress through school has been very satisfactory. She is now in the fourth grade, having made two grades in one year. She has always been very active physically. She is very

Figure 1—Comparison of Case 6106 at the age of 9 yr. 6 mo. with a normal boy of the same age.

limber, having some hyperextensibility of the joints. She has no disturbance of the special senses nor of the nonendocrine systems. She has always been considered strong and active for her age. She has studied French, makes good grades in arithmetic and is a voracious reader. She has read all fairy stories for children and is interested in mystery stories.

Examination.—General:	*Actual*	*Normal Variations* *Absolute*
Weight	27.5 lb.	53.6-67.2 lb. (absolute)
		25.3-31.5 " (relative)
Height	35.5 in.	50.1-53.7 in.
Span	35.2 "	49.6-53.4 "
Upper measurement	19.5 "	25.0-27.4 "
Lower measurement	16.0 "	24.6-27.0 "
Circumference of head	18.5 "	20.6 in. (opt.)
Circumference of chest	19.5 "	24.6 " (")
Circumference of abdomen	20.0 "	21.5 " (")

The stature was miniature, being the average size of a normal three-and-one-half-year-old child. The measurements were typically pituitary, the upper measurement being longer than the lower by 3.5 inches and the span height were almost equal. The head was large in proportion to the body. The skin was soft and thin. The hands were small, with some dorsal padding. A slight fullness was present in the supraclavicular region. There was a slight tendency to potbelly and the mammary region was full. Posteriorly, lordosis was positive. Peculiar folds were present just beneath and anterior to the axillae, resembling supernumerary mammae, but there was no evidence of nipples. There was some excessive hair growth on the terminal lower extremities. Both hands and feet were well formed and proportionate to the rest of the body. No pigmentations nor other abnormal general signs were visible. The intelligence was keen, the patient was alert, resourceful, and answered to questions with acumen, demon-

strating good association of ideas and memory. There was some freckling about the face and terminal extremities. The teeth were miniature in size and were deciduous except one and there was some separation and slight upper malposition. The temperature was normal, 98.6° F. The blood pressure was 80 (systolic) (taken by obliteration of pulse), and the pulse rate was 90.

The head was decreased in size, but large in proportion to the body. The face had a tendency to hexagonal form. The forehead was high and broad, lateral aspects vertical and the chin not prominent. The features were perfect, but small, although the nose was somewhat retrousse. The ears were well formed, with no developmental defects. The eye muscles showed good balance and there was no internal strabismus. The pupils were equal and reacted to light and accommodation. There were no thyroid signs present. The nose was somewhat retrousse but well aerated. The lips were not thick nor pouting. The deciduous group of teeth were present, except for one. The mucous membranes were normal in color. Considerable lymphadenoid tissue was present in the

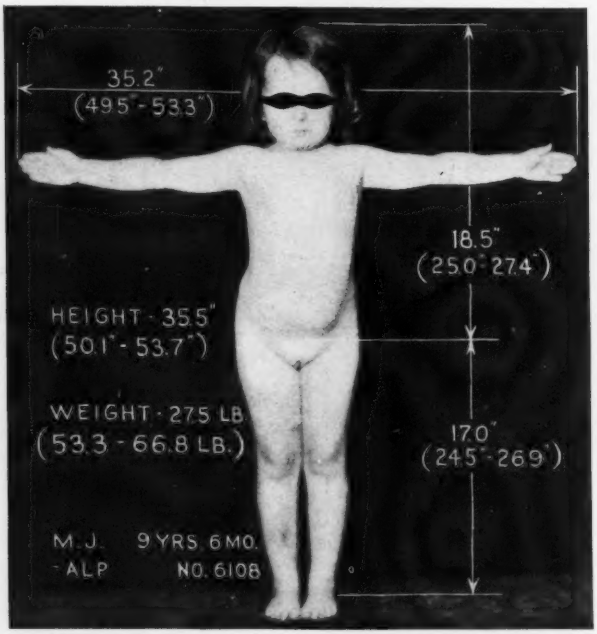

Figure 2.—Case 6106, hypopituitarism, aged 9 yr. 6 mo. Comparison of the actual figures with the minimum and maximum in parentheses. Note that all actual measurements are below the minimum for the age.

nasopharynx. The neck was short. Few lymph nodes were palpable and the thyroid was not palpable. The mammary glands were well developed but there were no secondary sex characters. The lungs and pleurae were normal and percussion resonant; there were no rales, rubs, nor other adventitious sounds. The apex beat was not wide nor heaving; there was no thrill, shock, nor bruit. Sounds at the apex were slow, pure and regular; the aortic and pulmonic areas were normal to auscultation. The abdomen was somewhat full, but there was no umbilical hernia. There was no increased resistance, tenderness, nor tumefaction. The liver dullness extended two fingerbreadths above costal arch to costal arch. The lower border was distinctly palpable below the costal arch. The spleen was not enlarged on palpation nor percussion. The kidneys were not palpable. The colon was normal and the inguinal regions negative. The external vaginal opening was normal and free from defects. The rectum was normal. Musculature was well developed in proportion to statural size. Large ecchymotic spots were present about the lower extremities (bruises easily).

Hypermobility of the joints was more marked in the upper extremities. She could bend the fingers back over the wrist. The reflexes were normal. Chvostek's sign was absent.

Laboratory findings.—The urine examination was negative except for a very faint trace of albumin and an occasional leucocyte. The blood examination showed hemoglobin, 66 per cent; erythrocytes, 3,600,000; leucocytes, 5,050. Differential analysis was: Polymorphonuclears, 30 per cent; small lymphocytes, 66 per cent; large mononuclears, 4 per cent. The red blood cells showed slight achromia. The Wassermann and Kahn tests were negative. The blood sugar was 120 mgm. per cent. The blood calcium was 11.03 mgm. per cent and the basal metabolic rate was 4 per cent. The blood test for anterior lobe sex factors (Dr. C. F. Fluhmann, San Francisco) was negative. In the roentgenographic examination the osseous centers of all joints showed epiphyseal development equal to 8 years or a delay in osseous development of at least one year. The sella turcica was small but normal for the size of the miniature head. The chest was normal except decreased in size. The heart was normal compared to size of chest but small for age. A seven-foot film for heart measurements gave the following dimensions: Chest, 15.7 cm.; MR, 2.8 cm.; ML, 5.0 cm.; TD, 7.8 cm.; LD, 8.7 cm.

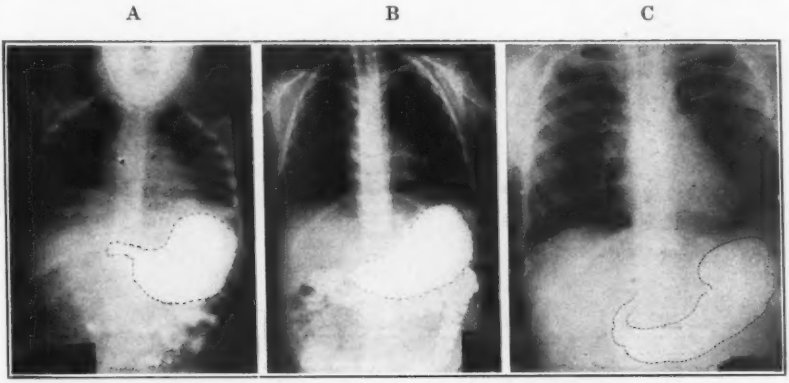

Figure 3.—Roentgen comparison of the size of the heart and stomach in (B) hypopituitarism, 9 years. 6 mo.; (A) normal, 2 yr. 4 mo.; and (C) normal, 9 yr. 4 mo. Note that the size of the heart and stomach in the hypopituitarism (B) at 9 yr. 6 mo. is less in size of a normal at 2 yr. and 4 mo. and equals only about one-half of the size of the normal of the same age.

The Diagnosis was hypopituitarism, evidencing since the age of six and almost complete deficiency of the growth hormone. Unless corrected there is a probability that at maturity there will be an associated deficiency of the pituitary sex hormone which will result in a postadolescent pituitary infantilism including hypofunction and aplasia of the genital organs.

Course and Therapeutic Reaction.—This case has been observed from October 31, 1930, and has been under treatment from December 4, 1930, to August 17, 1931. During this time she was given Evans' purified growth hormone from which the sex hormones had been separated. As this was the first human subject to receive this hormonic treatment, marked precautions were used in regard to its administration first by the writer and later by Dr. E. K. Shelton and Dr. Cavanaugh, who continued the treatment under the supervision of the writer. She was first given a number of intradermal injections of increasing amounts without production of local reactions. Then subcutaneous injections beginning with a one minim dose were gradually increased until she received one cc. There was a slight local reaction from the first few subcutaneous injections, after which they were absent until very large doses were administered. Following the determination that a one cc. dose was tolerated without untoward effect, the size of the dose was gradually increased until at present she is receiving nine cc. subcutaneously six days a week. The only untoward reaction that she has experienced has been a slight tenderness around the point of injection for a few hours and a very occasional rise of temperature to 99° F. which followed the

smaller as well as the larger doses. The following table compares her measurements previous to, and following, this treatment:

	October 31, 1930	August 17, 1931
Weight	27.5 lb.	35.0 lb.
Height	35.5 in.	38.2 in.
Span	35.2 in.	36.9 in.
Circumference of head	18.5 in.	19.1 in.
Circumference of chest	19.5 in.	21.2 in.
Circumference of abdomen	20.0 in.	21.3 in.

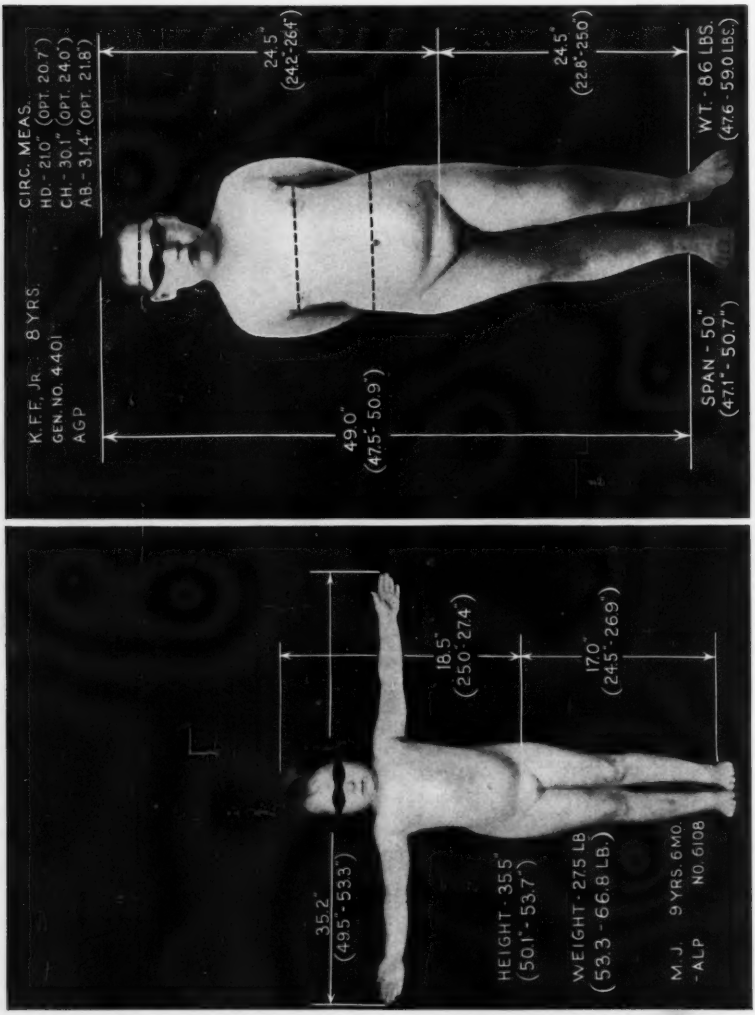

Figure 4.—Comparison of Case 6106, hypopituitarism, aged 9 yr. 6 mo., with Case 4001, hyperpituitarism, 8 yr. Note the measurements in the hypopituitarism are all below the minimum for age; whereas in the hyperpituitarism the measurements exceed the maximum for age. The development in the case of hyperpituitarism at the age of 8 yr. greatly exceeds that of the hypopituitarism a year and a half older.

It will be noted that from the above measurements there has been an increase of 2.7 inches in height; 7.5 pounds in weight; 0.6 inches in circumference of the head; 1.7 inches in the chest; and 1.3 inches in the abdomen. During the eight months and seventeen days of this treatment this is quite remarkable

considering the fact that there had been no increase in height during the four years previous to the treatment as determined by the parents by actual measurement. While there was more mature appearance and apparent redistribution of adipose tissue, no indication of primary or secondary sex development has appeared.

Analysis of Symptomatology and Diagnosis: The diagnosis of juvenile hypopituitarism is comparatively easily made by (a) the exclusion of all exogenous conditions producing retardation or undergrowth and (b) the demonstration of general underdevelopment by actual measurements. In the differential diagnosis of non-endocrine diseases producing underdevelopment is included the chronic infections and the deficiency diseases producing malnutrition. In addition, lesions of the non-endocrine systems such as the congenital cardiopathies must be considered. With the exception of hypothyroidism there are comparatively few endocrine disorders which produce the degrees of microsomia present in deficiency of the anterior lobe of the hypophysis. Hypothyroidism is readily excluded in the infantile and juvenile pituitarism by the lack of retardation of the osseous centers, mental defects, orthodontial and other regional and general hormonic signs of thyroidism that are absent in hypopituitarism. In the late juvenile years a secondary osseous retardation is present in the pituitary deficiency. This is due to the secondary hypothyroidism caused by the lack of growth hormone supplied to the thyroid gland. Following adolescence these primary pituitary insufficiencies progress into a pituitary thyroid disorder—pituitarothyroidism.

Positive Diagnosis: The family history of hypopituitarism usually reveals positive evidence of familial pituitarism such as infantilism gigantism, adiposogenitalism, genital aplasia, and in the female menstrual defects, chloasma, and vitiligo. On account of their inherent etiology the majority of these cases have shown retarded physical development and diminutive size during infancy, history of which is easily obtained by comparison with the normal children of their age. Such history in conjunction with actual measurements, all of which are below the minimum for the age, is usually sufficient to establish a positive diagnosis, provided other causes for underdevelopment and malnutrition are excluded.

Prognosis: Owing to the previous lack of knowledge concerning the cause of this infantilism, comparatively few of these cases are recognized in the juvenile or infantile periods. In addition to the failure of recognition, until the growth hormone had been purified, efficacious treatment has not been at hand. Consequently, up to this time the prognosis has been considered absolutely unfavorable with regard to production of growth or the subsequent development and genital function. Fortunately, now their diagnosis has been clarified and a specific treatment is available. Hence, in the future these hypopituitarisms should be among the most amenable endocrinopathies. Not only should the abnormal growth and development of the patients of the infantile and juvenile periods be overcome, but in addition their asexuality should be prevented by the provocation of ma-

turity and development of the genital system at the normal time, which in turn should maintain genital function throughout the later periods of life.

Treatment: The treatment of these infantile hypopituitarisms as those of all endocrinisms should be directed primarily towards their prevention and secondarily towards their cure. The prophylaxis of pituitary disorder pertains to parental treatment before conception or during gravidity. The occurrence of pituitary disorder among the children of a family should justify professional warning to both parents that they may have other children of their kind. This circumstance should instigate an investigation for endocrinopathies of the parents, correction of which would prevent the birth of subsequent ones. The treatment of adult pituitarism preventing this transmission as well as many other abnormalities of parents should be given for some time prior to conception. Next in importance are preventive measures during gravidity. During this time the response of the hypophysis to gravidity should be carefully investigated. Time will not permit a description of the lack of response of the hypophysis to pregnancy. Suffice here to say that an unusual increase of more than twenty-five pounds or less than fifteen pounds in weight during term or a failure to return to normal weight and figure following a previous gravidity, would be suggestive that the mother has had a partial pituitary insufficiency previous to conception, which prevented the hypophysis from reacting normally to the physiological demand of pregnancy. In addition the featural changes produced by subdermal thickening, minor osteophitic changes, and unusual distribution of chloasma would be additional evidence of transient pituitary disorder. The occurrence of other distressing symptoms, such as hyperemesis, albuminuria, and high blood pressure, in a positive pituitarism would be further indication of lack of pituitary response. It is questionable whether the oral administration of the anterior lobe preparations has any effect in these as well as other adult pituitarisms. There is no intrinsic contra-indication, however, to giving large doses, *e.g.*, five to ten grains, by mouth. These preparations certainly have no untoward reaction and possibly may be an adjunct to their hypodermic replacement. These easily recognized hormonic signs would indicate pituitary replacement treatment during pregnancy to prevent additional abnormalities of the mother and decrease the tendency to transmit the disorder to the offspring. The probabilities are that this deficiency affects the anterior lobe, whose growth and sex hormones are so necessary to the embryo, more than the posterior lobe. At any rate, the hormone from the posterior lobe, pituitrin, or at least its ocytocic fraction, pitocin, is contraindicated during pregnancy on account of its action upon uterine contractions which might produce premature labor. On the other hand, the extract of the anterior lobe given hypodermically would have no effect upon the course of pregnancy. The preventive treatment to the gravid mother as indicated by such symptomatology would be the replacement of alkaline extract

of the anterior lobe of the hypophysis until a purified preparation of these hormones is available. This is given in the form of alkaline extracts of the anterior lobe in rat units or antuitrin one cc. intramuscularly daily, or at least two or three times a week. The size of the dosage of antuitrin should be controlled by the production of headache, which results from an overdose of this extract. Should headache occur following the initial injection, the dose should be reduced below the amount producing such symptoms. The duration for this preventive treatment during pregnancy would depend upon reaction of the physical signs of a mild pituitarism, such as increase in weight, dermal-osseous changes, and chloasmic pigmentation.

The indication for treatment in the complete hypopituitarism having deficiency of both the growth and sex hormones of the hypophysis is that of replacing both of these hormones during the preadolescent years when they are necessary to fulfill their effects upon the non-endocrine organs of the body. The growth hormone should be supplied at the time its insufficiency becomes evident. This may be in the early years of juvenility or even during infancy. The opportune time for replacement of pituitary sex hormones is during the prepubescent years from eleven to thirteen, during which time they are normally released. The supply of the growth hormone is more essential during the first three years of life during which the child attains half of its height. Nevertheless its substitution during juvenility, as illustrated in Case 2, is yet able to produce marked somatic changes. It is probable that a replacement of either one of these hormones would be insufficient to procure the best result obtainable although there is a question whether the pituitary sex hormones are ever indicated before the age of ten or eleven. On the other hand, a simple substitution of the growth hormones early in life may of itself be all that is necessary to produce the cytological development of the hypophysis so that the basophilic and chromophobic elements are able at the time of the onset of adolescence to furnish sufficient pituitary sex hormones for the provocation of maturity. At any rate in positive cases of late juvenile pituitary infantilism better judgment would indicate a replacement of both the pituitary growth and sex hormones in order to procure the normal bodily development and genital function.

Preparation and dosage: Unfortunately at the time of this writing there are no purified preparations of either the growth or sex hormones, whose potency has been accepted by the Council on Pharmacy, on the market. Both these hormones will undoubtedly soon be placed at the disposal of the general practitioners. Evans' growth hormone, the first biological preparation isolated, and the one which has been demonstrated to produce the most positive reactions, would be the most acceptable one to use. Until this is available other alkaline extracts of the anterior hypophysis must be substituted. Among those having been demonstrated by assay to have growth properties is antuitrin. This extract as compared to purified Evans' growth hormone has been shown by animal experiments to

contain one-third to one-half of potency of Evans' purified hormone. It is given intramuscularly in one to two cc. doses until cranial fullness and headache is produced. These symptoms should indicate the size of a tolerable dose. As stated previously, these untoward effects may be due to amino acid which later purification may withdraw. Larger doses—five cc.—intravenously have caused no serious untoward effects. In fact, no allergic or other unfavorable results have been obtained from many years' use of this preparation. Tethelin (Robertson) has been shown by assay to have comparatively little or no effects upon growth or development. Similarly clinical use of this preparation has not been productive of results obtained from Evans' growth hormone or antuitrin.

The sex hormones of the pituitary gland are derived by acid extraction of the anteropituitary or the urine of pregnant women. Prolan A and B (Zondek), the sex hormones extrated from the urine, have not yet been marketed in this country. Prolan A and B are given hypodermatically in one to five cc. doses. Other preparations coming on the market will probably be estimated by their specific reactions as measured by rat units. The interval and the continuation of these treatments should be determined by the effects they have upon the deficient hormonic signs of this disorder. Those of the growth hormone can be simply measured by anthropometric determination. Those of the sex hormone will depend entilely upon the development and function of the genital system. Discontinuance of both growth and sex hormones may be made after the individual has arrived within the normal variations of measurements. The continued use of the sex hormones is determined by time of maturity and the postadolescent maintenance of genital function and the development of the genital system. After both of these requirements, normal physical development and genital development and function, have been obtained there are no further indications for replacement of these hormones.

SUMMARY

The author reports two cases of hypopituitarism, showing marked deficiency of both the growth and sex hormones. One subject of infantile hypopituitarism is four years of age, and the other is a juvenile aged nine years and six months. This subject was given replacement treatment of Evans' purified growth hormone. Although Evans discovered the growth hormone in 1922, this is the first human being to whom it has been given. This has been due to the difficulties in its purification and separation from the pituitary sex hormone. This paper discusses the incidence, symptomatology, and diagnosis, as well as the treatment of insufficiency of the anterior lobe of the hypophysis during the preadolescent age. The auther contends that hypopituitarism during infancy and juvenility is a very common endocrine disorder. Emphasis is placed upon the case of diagnosis of deficiency of the growth hormone, which is made by comparison of actual measurements of infants and juveniles with standard measurements

for age and sex, such standard measurements being included in this article. The subject who was given replacement of Evans' growth hormone was a girl nine years and six months of age who had had an arrested physical development for a number of years previous to institution of such treatment. This hormone, which Professor Evans had tested out very carefully by prolonged animal experimentation, was given first in very minute doses and gradually increased until 10 cc. was given intramuscularly. The reaction to this treatment during the nine months and seventeen days that it was administered showed that there was an increase of 2.7 inches in height; 7.5 pounds in weight; 0.6 inches in circumference of the head; 1.7 inches in the chest, and 1.3 inches in the abdomen. The reaction to treatment during this age is very favorable.

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NODULAR HYPERPLASIA OF ADRENAL MEDULLA IN HYPERTENSION

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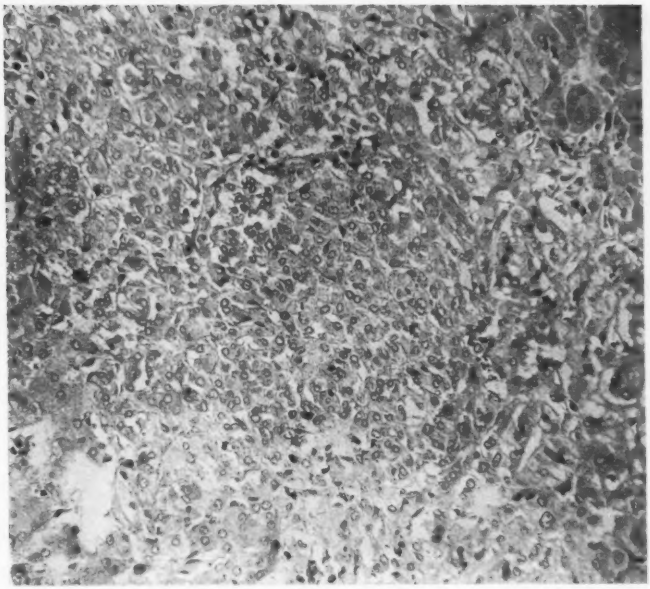
In recent years several new cases of phaeochrome tumors have been described which occurred in patients with symptoms of severe hypertension, hypertrophy of the left ventricle and arteriosclerosis. As far as I was able to ascertain, there were 42 cases reported, 34 of which were recently reviewed by Rabin and 6 additional cases by Labbe. Most important in this series are the cases of Mayo, Shipley and Porter in which the diagnosis of a phaeochrome tumor was made during life and surgical removal was resorted to. All three patients recovered from their symptoms after operation. This seems to speak rather strongly in favor of the conception that an excessive amount of phaeochrome tissue such as represented by these tumors, is capable of producing symptoms of hypertension and leaving in its wake lesions of arteries. It seems difficult to dismiss such weighty evidence merely because demonstration of hyperadrenalinemia in hypertension has not been successfully made.

The role of the adrenals in the pathogenesis of hypertension and arteriosclerosis was first stressed by Josué and the French school and by Wiesel. The author tried in a monograph (1911) to add further proof to this conception and has continued in this endeavor during the past 20 years. The evidence thus accumulated has been summarized lately as follows: Increased adrenalin content of the glands (Goldzieher, Ingier and Schmorl); hypertrophy of the musculature of the adrenal veins (Goldzieher and Sherman, Allen); morphological changes of the adrenal cortex (Landau); diffuse hyperplasia of the adrenal medulla (Wiesel, Goldzieher).

In a recent report on several cases of hypertension, it was shown that besides diffuse hyperplasia of the medulla there were also nodules of phaeochrome tissue present which were quite comparable to the nodular growths characteristic of hyperplastic processes in other glandular organs. Since we became familiar with this type of nodular hyperplasia, we have been fortunate enough to recognize such lesions with increasing frequency. It seems justifiable, therefore, to draw the attention to these changes in order to establish whether their occurrence in hypertension is only incidental or might be expected with a degree of regularity.

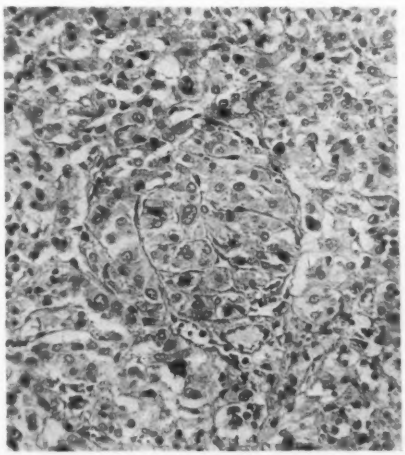
The following is a brief description of four recently observed cases:

1. John R., 55 years of age, was admitted January 11, 1931, with a history of swelling of the abdomen and ankles. Dyspnea and anorexia had been increasing lately. After admission 4000 cc. ascitic fluid was removed by abdominal tap. During his stay at the hospital the abdomen was tapped two more times, and 3000 cc. of the fluid was removed at one time and 4000 cc. at another. The patient was jaundiced and showed an icteric index of 28. His urine



1.—Case No. 2. Small nodule of the adrenal medulla surrounded by medullary tissue with wider capillaries.

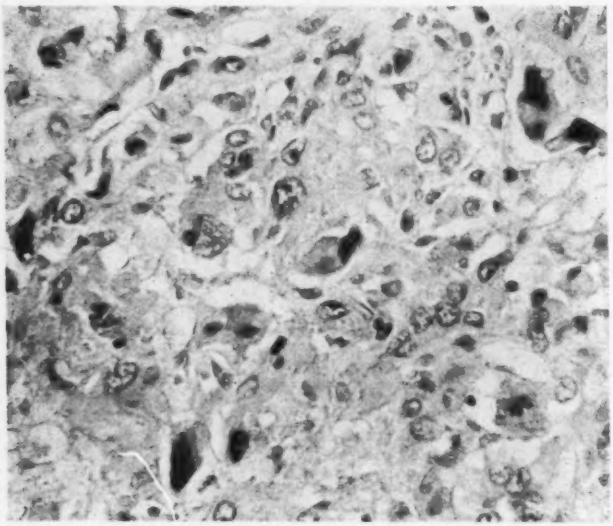
was of high specific gravity, varying from 1020 to 1026. Blood examination showed a moderate anemia with 3,600,000 red blood cells, 70 per cent hemoglobin and 6800 white cells. The blood chemistry was normal, the Wassermann reaction negative, and the temperature fluctuated between 98 and 100. The liver and spleen could not be palpated, because of distension. The absence of hair over the chest and extremities was striking. The diagnosis of atrophic liver cirrhosis was made. The patient died January 27, 1931.



2.—Case No. 2. Small nodule of the medulla of concentric structure.

Autopsy (Rec. No. 311) revealed an atrophic cirrhosis of the liver with splenomegaly and ascites, sclerotic changes of both the aorta and peripheral arteries, small atrophic thyroid and testicles, hypertrophy of prostate, and adrenals of medium size.

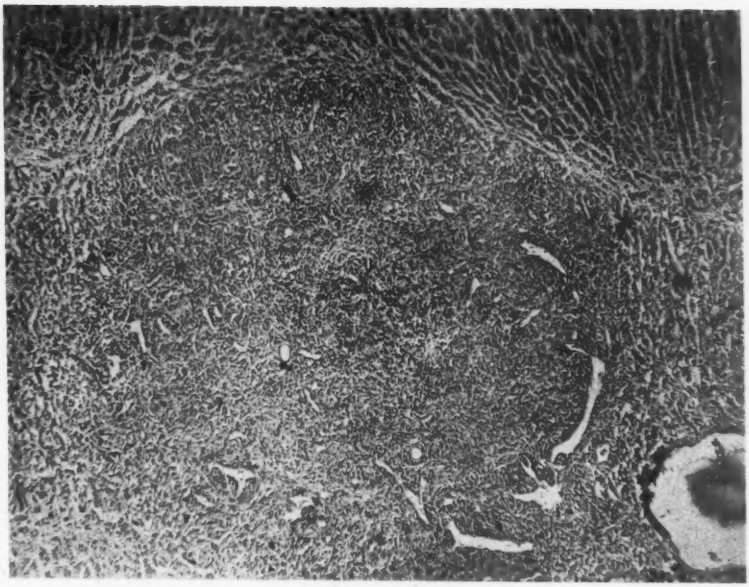
The microscopical examination showed all three layers of the cortex to be well developed. There was a large amount of lipoid present. Its irregular distribution accounted for the peculiar, almost nodular structure of the cortex. The medulla was abundant; it was of trabecular structure with wide capillaries between the massive strands of medullary cells. There was one nodule about 1½ mm. in diameter which distinguished itself from the adjacent medullary tissue by greater cellularity, denser structure, comparatively scanty and narrow blood spaces and smaller size of its cells. The cytoplasm of these cells also stained somewhat less intensely than that of the surrounding medullary tissue. The most important feature of this nodule, however, was the size of the individual trabecles found between two blood spaces. Eight to 10 rows of cells formed some of these trabecles as compared with 1 to 3 in the ordinary medulla.



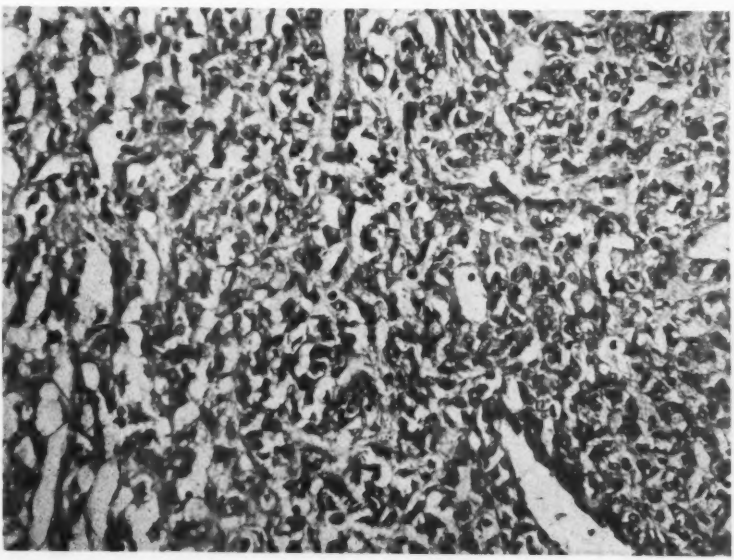
3.—Case No. 2. Polymorphous and hyperchromatic nuclei of the medullary cells.

There was a diffuse hyperplasia of the medulla to be noticed outside of the nodule. Some of the trabecles were more than twice as thick as usual. The individual cells were polymorphous, their cytoplasm was basophilic and many of the nuclei were irregular in size, shape and also in chromatin content. There was a marked hypertrophy of the musculature, both in the smaller and larger veins.

2. Michael G., 59 years of age, was admitted January 7, 1931. His previous history was negative. He did not smoke nor use alcohol. He complained of a cough which he had had for the past two years and dyspnea on exertion. His appetite was poor and he vomited daily in the morning. There was pain in the epigastrium. He had lost 15 pounds weight during the last few months and also had observed recently blurring of vision. The skin was a bronze color, particularly over the face and both extremities. There was no pigmentation of the mucous membranes. The heart was enlarged to the left. The blood pressure was 165/95. The urine showed a fixed specific gravity of 1010 with two plus albumin and occasional red cells. The blood chemistry showed urea 120, creatinin 5.5, and glucose 100. Repeated chemical studies always showed very high figures for urea, which, however, declined to 65 terminally. The blood count showed 2,280,000 red blood cells and 70 per cent hemoglobin. The patient died on the 17th day after admission.



4.—Case No. 3. Larger nodule of the medulla compressing the adjacent cortical tissue. (Low power.)

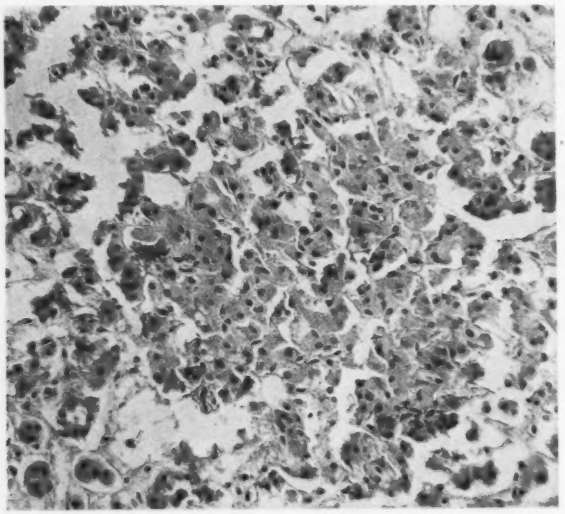


5.—Case No. 3. A part of figure 4 under high power magnification. Note the denser structure of the nodule compared to the adjacent medullary tissue with its numerous wide capillaries.

Autopsy (Rec. No. 309) showed generalized arteriosclerosis with marked calcification, extending from the aorta over to the aortic valves. The kidneys showed granular atrophy and patent, rigid arteries on section. There was a substantial hypertrophy of the left ventricle. The adrenals were medium sized, firm and grossly unchanged in appearance.

The microscopical examination showed the cortex to be well developed and containing ample lipoids. The medulla was very abundant and consisted mostly of large polyhedral cells with narrow blood spaces in between. The medullary tissue had a tendency to grouping into nodules which differed from the rest of the medullary tissue by their greater cellularity, denser structure, narrower blood spaces and a much more irregular architecture. These nodules appeared almost solid in places, while occasionally an alveolar structure was seen. The individual cells were large and polyhedral, and their nuclei were large and vesicular. Some of the nodules also showed a number of hyperchromatic nuclei of irregular shape and often unusual size. The musculature of the veins was hypertrophic and particularly the central vein showed a greatly thickened wall.

3. Abraham A., 40 years of age, was admitted April 2, 1931. He had suffered for quite some time from polydypsia and polyuria. He had lost a small amount of weight during the last two years. Recently he had been bleeding a



6.—Case No. 4. Small nodular aggregation of large polyhedral medullary cells.

good deal from the nose and developed a temperature which rose the day after admission to 106. His urine was normal and so was his blood chemistry. The pulse rate was 130. The blood pressure varied between 88/64 and 115/60. Blood examination revealed evidence of a severe aplastic anemia. The patient died on the 8th day after admission.

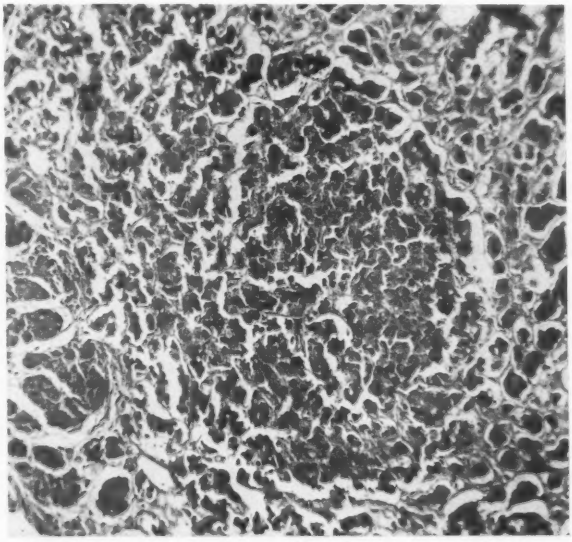
Autopsy (Rec. No. 334) showed fatty bone marrow throughout. There was pigmentation of the spleen and liver; sclerosis of the peripheral arteries; brown atrophy of the heart muscle. The adrenals were rather large and firm. The cortex was bright yellow in color. The silver-gray medulla was abundant on section.

The microscopical examination showed the cortex to have all three layers well developed. The medulla was unusually massive and showed evidence of diffuse hyperplasia. The nuclei of the medullary cells were irregular and often hyperchromatic, while their cytoplasm was intensely basophilic. Some of the cells formed larger syncytial groups. There was a large nodule in the medulla about 3 mm. in diameter. It could be recognized on section without a microscope by its darker blue color. This appearance was due to the greater cellularity of the nodule and to the presence of but scanty and narrow capillaries. The cells of the nodule were conspicuously more polymorphous and the

nuclei more hyperchromatic. Some of the nuclei were gigantic in size. The musculature of the veins showed definite hypertrophy.

4. Ida F., 46 years of age, had been repeatedly at the hospital, with a chronic kidney condition. She was readmitted on December 22, 1930, seven days after her last discharge from the hospital. She complained of headaches, nausea and swelling of the ankles. Her heart was enlarged to the left, with a systolic blow at the apex. The second pulmonic sound was accentuated. The blood chemistry showed a urea varying from 45 to 70 and creatinin 3 to 4.5. There was a secondary anemia with 2,250,000 red cells. The urine showed albumin but no casts nor red cells. Its specific gravity was fixed at 1010. The patient developed cerebral symptoms and died on April 20, 1931 in coma. Her blood pressure during her stay at the hospital varied from 235 to 248 over 130.

Autopsy (Rec. No. 342) showed advanced vascular sclerosis of the kidneys (granular atrophy); arteriosclerosis of the aorta and peripheral arteries, particularly of the cerebral arteries. There was hypertrophy of the left ventricle and destructive hemorrhage of the right cerebral hemisphere. There was evidence of old rheumatic endocarditis with mitral stenosis, and terminal bronchopneumonia. The adrenals were fairly large, particularly the left gland. They



7.—Case No. 4. Small solid nodule adjacent to the wall of a larger vein.

were firm on touching, their cortex slightly nodular and of intense yellow color. The medulla was quite abundant on section.

The microscopical examination showed the cortex to have three well developed layers with comparatively little lipoid substance in the well stained cortical cells. The medulla was fairly abundant and formed an irregular trabecular structure. The medullary cells were of two different types; one was small, while the other type was very large and polyhedral. The latter cells occasionally form definite groups which are distinct from the surrounding medullary tissue. Next to the wall of the central vein there was a definite nodule which was apparently oval in shape, as shown on serial sections. The cross section of the nodule was almost round; the cells were quite densely packed with very narrow and often collapsed blood spaces in between. The nuclei of these and the other medullary cells were rather small, round and hyperchromatic.

COMMENT

In each of the four cases described there was one or more nodules present associated with diffuse hyperplasia of the medulla. All cases also

showed hypertrophy of the musculature of the adrenal veins. In three of these cases some of the nuclei of the phaeochrome cells showed such irregularities of size, shape and chromatin content as are found usually in neoplastic or other rapidly proliferating tissues.

Two of these cases, clinically, gave evidence of high blood pressure. No note of blood pressure was available in the case of liver cirrhosis, but advanced sclerosis of the aorta and the peripheral arteries is indicative of hypertension having existed at least at some time previously. Low blood pressure of 88/64 and 115/60 was noted in the fourth case. The patient died from an anemic condition on the 8th day after admission. Letting down of the blood pressure in such a state might be expected. This patient also showed sclerosis of the peripheral arteries. In a man 40 years of age this seems to indicate that hypertension was present prior to his terminal debilitated condition and the development of brown atrophy of the heart.

DISCUSSION

While the previously offered evidence as to the hyperplasia of the adrenal medulla in hypertension was not sufficiently convincing and in certain points (Wiesel's sympathogones) was open to challenge, the contention of a diffuse hyperplasia is supplemented now by demonstration of hyperplastic nodules of the medulla. The polymorphous appearance of these cells, the morphology of their nuclei including the presence of some gigantic specimens, is well comparable to that of the cells in hyperplasia of other glandular organs. The increased adrenalin content of the adrenals in hypertension and particularly the hypertrophy of the musculature in the wall of the adrenal vein seems to prove that functional hyperactivity is concomitant. This would seem obvious in view of the fact that hyperplasia of other glandular organs is, as a rule, considered adequate morphological evidence of their increased function.

It might be expected in view of the preceding considerations that the clinical manifestations of nodular hyperplasia of the adrenal medulla do not essentially differ from those observed in cases of phaeochrome tumors. Quantitative differences are likely to exist and explain the rapid progress, paroxysmal character and early fatal outcome of the tumor cases, in contradistinction to the insidious onset, slow progress and protracted course of hypertensive disease in the presence of nodular hyperplasia of the adrenal medulla.

Experimental work done during the past ten years has produced what some physiologists believe to be weighty evidence that the physiological significance of the adrenal medulla is negligible and the phaeochrome tissue ranks in importance somewhere with the appendix. Cannon and his coworkers successfully contradicted these statements and showed the great emergency value of the adrenal medulla. Recent experiments by Vincent and Thompson have uncovered some of the errors in the technique of earlier experimenters. They showed that ligation of the adrenal vein can not produce a substantial drop in blood pressure on account of the collateral circu-

lation which drains the blood of the adrenal after obstruction of the main vein. Ligation of these collaterals together with the main veins produces the expected fall in blood pressure which the earlier investigators failed to obtain. Another recent addition to our knowledge of adrenal physiology must be credited to Dragstedt and co-workers, who showed that results obtained with injection of adrenalin in narcotised animals are rather misleading. It could be demonstrated that irritability of the arterial musculature is considerably decreased by narcosis, while the effect of the latter upon the intestinal musculature is by far less accentuated. Thus one of the main arguments crumbles, the one which had been advanced to prove that adrenalin discharged by the adrenals cannot have any effect upon blood pressure. The value of this contribution is even greater in its general aspects: it teaches us to be wary of complicated physiological experiments which crudely try to imitate pathological phenomena. The result of such experiments should be taken *cum grano salis* if it contradicts clinical and morbid anatomical evidence.

The conception that pathological changes of the adrenals had anything to do with hypertension was mostly frowned upon during the last decade. In France, however, numerous prominent clinicians, and particularly Vaquez, firmly maintained such a viewpoint. Recently Volhard and R. Schmidt, among other leading German physicians, also considered pathological function of the adrenals as one of the possible factors in the pathogenesis of hypertension. Schultz noticed the unusually rich adrenalin content of a tumor which had been removed from a patient suffering from periodic hypertension amounting to as much as 260 mm. blood pressure. Wilder in commenting upon several cases of phaeochrome tumors, emphasizes the role of hyperepinephrinism in certain forms of hypertension. Rowntree quite recently maintained similar views. Thus the conception of adrenal hyperfunction as one of the underlying factors in the pathogenesis of hypertension seems to overcome the obstacles which were raised against it by dogmatic physiological research. Further anatomical studies will have to determine how regularly the changes described in this paper are associated with hypertension.

SUMMARY

Attention is called to the occurrence of nodular hyperplasia of the adrenal medulla in cases of hypertension and arteriosclerosis. Four new cases are described. The significance of adrenal hyperfunction in the pathogenesis of hypertension is emphasized.

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HYPERINSULINISM AND DYSINSULINISM (INSULOGENIC HYPOGLYCEMIA)*

WITH A CHRONOLOGICAL REVIEW OF CASES REPORTED IN THE UNITED STATES AND CANADA.

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Insulin is a true internal secretion derived from the ductless glands (islands of Langerhans) of the pancreas. Like other glands of internal secretions, i. e., the thyroid, the suprarenals, the pituitary bodies, etc., the islet cells of the pancreas, because of various functional or pathological changes, may function excessively or deficiently. The part which the internal secretion of the pancreas (insulin) plays in carbohydrate metabolism is well known. When there is a deficiency of insulin with defective carbohydrate metabolism there accumulates in the blood an excess of sugar (hyperglycemia), a part of which is excreted by the kidneys (glycosuria). Tradition tells us that the ancients observed bees swarming around the "sweet" urine of patients who also had the syndrome of polyuria, thirst, hunger and emaciation, and they called the disease diabetes mellitus.

If diabetes had been discovered since our present nosology of disease has been accepted it would be called hypoinsulinism, because that name identifies it with a deficient secretion of the ductless glands of the pancreas, just as a deficiency of the internal secretion of the thyroid (thyroxin) is called hypothyroidism, and as the symptom syndrome resulting from a deficient secretion of the pituitary bodies is called hypopituitarism, and as the deficient secretion of the suprarenals (epinephrin) is called hypoadrenalism. Even now some authors are using hypoinsulinism as a substitute for the term diabetes mellitus. Trumper and Cantarow (1) discuss diabetes mellitus under the title of hypoinsulinism.

The discovery of insulin by Banting and Best (2), and their observations, with those of Macleod and Noble (3) and Campbell and Fletcher (4), that overdoses of insulin administered hypodermatically produce hypoglycemia, with definite symptoms, were responsible for the assumption by the writer that the islet cells of the pancreas may secrete an excess of insulin; and the work of those men made possible the discovery that spontaneous pancreatogenic hypoglycemia, with the characteristic symptoms of the insulin reaction (hyperinsulinism) exists as a disease entity. The writer (5) in 1923 observed non-diabetics who had symptoms identical with those resulting from an overdose of insulin; and reasoning that the increased secretion of insulin by the islands of Langerhans was analogous to the overproduction of thyroxin by the thyroid gland (hyperthyroidism),

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epinephrin by the suprarenals (hyperadrenalism), and pituitrin by the pituitary bodies (hyperpituitarism), he gave the hypoglycemia syndrome resulting from the overproduction of insulin by the islands of Langerhans, the name hyperinsulinism. Likewise, observing spontaneous hypoglycemia associated with symptoms identical with the insulin reaction in a diabetic who had never taken insulin, the term dysinsulinism was coined as applicable to cases of dysfunction of the insulinogenic organ resulting in hyperglycemia alternating with hypoglycemia. Hypoinsulinism (6) was suggested as the term best descriptive of the disease (diabetes mellitus) resulting from deficient secretion of the islands of Langerhans and characterized by hyperglycemia, glycosuria, polyuria, polydypsia, polyphagia, emaciation and weakness.

The First Reported Cases of Hyperinsulinism.

The first case (5) diagnosed as hyperinsulinism was that of a physician, aged 60, who came in for re-examination on April 27, 1923, presenting the same symptoms he had given in March, 1923, *i.e.*, weakness, nervousness and irritability about an hour before dinner and supper, relieved by taking a soft drink. His blood sugar an hour before his noon meal was 0.065 per cent. He also complained of wakefulness and the same symptoms at night. He gave a history of the excessive use of sweets, particularly soft drinks between meals. He was placed on a relatively low carbohydrate diet consisting largely of five and ten per cent vegetables and fruits, omitting cane sugar products altogether, with frequent meals; and orange juice or milk every two or three hours between meals, and when awake at night. His hypoglycemic symptoms subsided immediately, though 17 days later his fasting blood sugar was still low, 0.070 per cent. A diagnosis of mild hyperinsulinism was made. He continued the diet and at the end of a year had had no symptoms. He died about four years later after a prostatic operation.

The next case (5), presented more serious symptoms. A laborer, aged 52, had been treated in our Clinic for bronchitis, colitis, and protean digestive disturbances at various times since April 6, 1917. He returned for examination on October 5, 1923, complaining of excessive hunger, marked weakness, amounting at times to actual prostration, profuse perspiration, trembling, anxiety and marked nervousness coming on three or four hours after meals, and lasting until the next meal when he would get complete relief. He would awaken during the night because of weakness, coldness, sweating and nervousness. His fasting blood sugar when he was having symptoms of hypoglycemia was 0.065 per cent. A glucose tolerance test (50 grams of dextrose) showed the following hourly blood sugar readings: 0.098, 0.116, 0.169, 0.067 per cent with a trace of sugar in his urine at the end of the second hour when his blood sugar was 0.169 per cent. At the end of three hours when the patient left the Clinic his blood sugar was 0.067 per cent. He felt weak but did not complain, but an hour later on the trolley, before he could get home, he became so weak he could hardly get off the car. He was promptly relieved by taking food. In addition to the hyperinsulinism this patient was considered as a potential diabetic and placed on a low carbohydrate, high fat diet. He had no symptoms so long as he remained on this diet, but after a few years he became careless about his eating and began having more "hungry spells," as he called them. Finding that he could prevent and get relief from them by eating candy, he kept chocolate bars in his pocket constantly and ate freely of them between meals. On December 3, 1930, he returned again complaining of "hungry spells," two or three times a day, usually two or three hours after meals, associated with weakness, trembling and profuse perspiration. He had had a trace of sugar in his urine at times since 1923. On May 25, 1931, a glucose tolerance test was as follows: 8:00 A.M., fasting blood sugar, 0.070 per cent. He was then given 100 grams dextrose. At 9:00 A.M. his blood sugar was 0.085; at 9:30, 0.089; at 10:30, 0.085; at 11:30, 0.050; at 12:30, 0.050 per cent. when he began having symptoms of hypoglycemia, which were relieved by a glass of malted milk. He showed traces of sugar in his urine when his blood sugar was 0.085. 0.050 and 0.050. This observation suggests that a "low renal threshold" may be pancreatogenic in character.

It will be noted that this patient who has been under observation for eight years can control his hyperinsulinism by dieting just as the diabetic controls, but does not cure his disease, by dieting. This observation suggests a permanent lesion of the pancreas as the etiologic factor in this case.

These two cases were reported first in 1923, and published in 1924 (6). The suggestion was made that hyperinsulinism may precede hypoinsulinism (diabetes mellitus) as hyperthyroidism is sometimes followed by hypothyroidism. In so far as can be learned, this is the first time the words hyperinsulinism and hypoinsulinism appeared in medical literature. Joslin in the last edition of his book, "Treatment of Diabetes Mellitus," (12) in discussing hyperinsulinism (p. 97) reviews the writer's report of the first cases.

Dysinsulinism

The first case diagnosed as dysinsulinism was in January, 1924. It was that of an obese woman who, a year before when she weighed 210 pounds, had had sugar in her urine. She was sent to us as a diabetic. She had reduced, by dieting, to 160 pounds and complained of having "spells of weakness and nervousness" at about one or two o'clock at night. She had found from experience that eating would relieve the symptoms, so that she kept an orange or a glass of milk on the table by her bed. Her fasting blood sugar was 0.047 per cent. She was relieved promptly by frequent feedings of a low carbohydrate diet, consisting largely of the five and ten per cent vegetables and fruits with sufficient proteins and fats.

Joslin (7) in 1921, before the discovery of insulin, reported the deaths of two diabetics that occurred while on a very low carbohydrate diet (about 900 calories a day), in which the blood sugar dropped to very low levels shortly before death, i.e., 0.050 and 0.040 per cent. Joslin attributed the hypoglycemia and the deaths of the two diabetics to undernutrition. He did not suggest overactivity of the islands of Langerhans as a cause of the hypoglycemia, nor did he offer any other explanation for the phenomenon of rapidly falling blood sugar. In commenting on these two cases he said, "the discovery of the presence of hypoglycemia during the course of treatment (of diabetes) by undernutrition is a danger signal of first importance."

It seems probable that with our present knowledge of the insulinogenic function of the pancreas the two cases reported by Joslin in 1921 would be considered of the type of disturbed function of the islands of Langerhans now called dysinsulinism. In the last few years several similar cases have been reported and the low blood sugars have been attributed to hypersecretion of insulin [Jonas (8), John (9), Harrop (10)].

BLOOD SUGAR READINGS IN STARVATION

The question as to whether the low blood sugar readings in the first cases reported were due to a lack of food, or to hyperinsulinemia with resulting hypoglycemia, was considered in the first paper on hyperinsulinism (5). If due to a lack of food, starving patients should show a low blood sugar. We chanced to have had in 1923 and in 1924 four patients who literally were starving to death. Three were cases of carcinoma with almost complete occlusion of the esophagus. All three patients were very much emaciated, and had been unable to take but little food for weeks or months before they came to us. None of them gave a history of symptoms of hypoglycemia. The fasting blood sugar readings on these three patients were 0.090, 0.084, and 0.090 per cent. About the same time we also had a patient who had almost complete stenosis of the pylorus due to a neg-

lected duodenal ulcer. The roentgen ray examination showed 90 per cent retention of the barium meal in six hours, and 75 per cent retention in twenty-four hours. This patient had vomited practically everything she had eaten for weeks and was in a state of marked emaciation. The blood sugar was 0.079 per cent.

It seems that in starvation the amount of sugar in the blood is kept within the normal range by endogenous katabolism. In the four cases of starvation we have reported apparently the amount of glucose derived from the katabolism of the protein and fat of the patient's own tissues was sufficient to keep the blood sugar above the point at which hypoglycemia reactions occur. Since in the starvation cases the blood sugars were within the low normal range, and none of the four patients had symptoms of hypoglycemia, and the hyperinsulinism patients having blood sugars below 0.070 per cent with few exceptions had symptoms of an overdose of insulin, it surely seems that the hypoglycemia in the cases we have reported was due to the excessive secretion of insulin, with rapid carbohydrate metabolism, thus reducing the sugar content of the blood.

ROUTINE BLOOD SUGARS ON NON-DIABETICS

The cases of hyperinsulinism with blood sugar findings below 0.070 per cent studied in 1923 and 1924 (5) stimulated us to undertake further studies of the blood sugar at the fasting period in non-diabetic patients. It should be remembered that most of our patients are adults who come to us for treatment of gastro-intestinal or nutritional disturbances; and most of these in our first series were ambulatory cases, though some of them required hospitalization. Blood sugar determinations were made on 253 patients in 1923 and 1924, 92 of whom were diabetics, who showed varying degrees of hyperglycemia. Of the 161 non-diabetics twelve patients had blood sugar readings of below 0.070 per cent in specimens obtained during the fasting periods; and all of these, with two or three exceptions, had symptoms that could result from hypoglycemia.

Since 1924 we have continued blood sugar determinations as a routine in the examination of our patients much of the time, and have records of the fasting blood sugar readings of 1867 patients. Of this number 370 were diabetics and all showed hyperglycemia, as is to be expected in hypoinsulinism. Fasting blood sugar readings above 0.120 per cent were found in 51 of the 1497 non-diabetics. These we classed as potential diabetics since the fasting hyperglycemia indicated a low carbohydrate tolerance likely due to the deficient secretion of insulin. They were dieted accordingly and we hope that we may have prevented diabetes in some of them.

Of the 1497 non-diabetics, 67 showed hypoglycemia of varying degrees, *i. e.*, 46 between 0.070 and 0.079 per cent; 17 between 0.060 and 0.069 per cent; one, 0.056; one, 0.50; one, 0.047; and one, 0.045 per cent. Most of the patients whose blood sugars were between 0.070 and 0.079 had mild symptoms of hypoglycemia, but in only five were the symptoms sufficiently

pronounced to make a diagnosis of hyperinsulinism. Nearly all of the 17 with blood sugar readings between 0.060 and 0.069 per cent had symptoms of hypoglycemia, but in only five were they sufficiently severe to make the diagnosis of hyperinsulinism; one of these, an 18-year-old boy, with blood sugar readings of 0.060 per cent, had recurring attacks of unexplained unconsciousness with convulsions. The patients with blood sugar readings of 0.056, 0.050 and 0.047, respectively, had marked symptoms of hypoglycemia. In one obese subject, with blood sugar of 0.045 per cent associated with marked lipemia, there were no symptoms suggesting hypoglycemia.

There were no evidences of liver or adrenal involvement in these cases, so it seems unlikely that the low blood sugars could have been due to impaired formation, or decreased lability, of glycogen. The inference, therefore, is that the hypoglycemia was due to excessive secretion of insulin, and that the pancreas is the seat of the pathologic or functional changes involved in the disease, or condition, now known as hyperinsulinism.

CHRONOLOGICAL REPORT OF OTHER AMERICAN CASES

Since the publication of the reports of our first cases of hyperinsulinism in 1923 and 1924, a number of cases have been reported in the United States and Canada, and in other countries, particularly Germany and Austria; and much excellent work has been done by a number of clinicians and pathologists, proving that the disease entity of hyperinsulinism exists, and that in some cases there is a pathologic basis for its existence. A chronologic review of the American cases reported by various clinicians presents many of the salient known facts regarding the symptoms, pathology and treatment of hyperinsulinism and dysinsulinism.

Gibson and Larimore (11), in November, 1923, observed, in giving glucose tolerance tests to two "renal diabetics," that the last readings were below normal, 0.062, and 0.040 per cent and that an hour later one patient had a "mild hypoglycemia reaction." When questioned as to the occurrence of similar attacks at home, the patient stated that she "had experienced such of milder degree," but could not associate them with any definite circumstances. One sister had like attacks. Gibson and Larimore added: "It seems likely that hypoglycemia symptoms not artificially produced are a definite clinical entity." They gave as an explanation for the phenomena in "renal diabetes," "rapid removal of glucose from the kidneys," but added, "repeated administration of glucose might so stimulate the glycogenic power that a normal or sub-normal sugar curve will result."

Jonas (8), in November, 1924, in a clinic on hypoglycemia, cited a case reported by Hartman and Reimann of a man who "suffered from hunger and marked weakness three or four hours after meals. On several occasions he became unconscious. The blood sugar during the attacks was below normal. Frequent feedings during the twenty-four hours relieved him of symptoms and permitted him to enjoy good health." Jonas also reported the occurrence of "spontaneous hypoglycemia" in a diabetic a number of days after insulin therapy was discontinued. Eleven days after insulin was discontinued the patient, a negro man, suddenly became delirious and then comatose, his blood sugar 0.030 per cent. He was given glucose intravenously and became conscious almost immediately. Several hours later he again became comatose, and died.

In February, 1925, John (9) reported a case of "hyperinsulinism" in a diabetic which he thought was due to the excessive use of insulin, attributing the hypoglycemia to the "prolonged effect of the insulin," which had been administered hypodermatically. In a later paper, John (13) reported that in this

same case, though insulin had been discontinued, the blood sugar remained low. John, in the same article, reported a case of spontaneous hyperinsulinism. Observing that following glucose tolerance tests there appeared in a number of cases very low blood sugar values: 0.031, 0.036, 0.040, 0.045, 0.048, 0.049, 0.050, 0.057 per cent, John (14) concluded that "the phenomenon must be due to some irregularity or oversensitiveness of the insulogenic regulating mechanism." John offered a plausible explanation of inducing hyperinsulinism, with resulting hypoglycemia, by the excessive use of carbohydrates. He said: "By overwhelming the organism with a large dose of carbohydrate the insulogenic organ (the islands of Langerhans) is overstimulated and throws a large amount of insulin into the blood stream, which in turn causes a rapid combustion of glucose circulating in the blood stream, so that the glucose output from the liver does not keep pace with the glucose consumption and hypoglycemia results." John later expressed the opinion that hyperinsulinism from the overingestion of carbohydrates. thus exhausting the islet cells, is an important etiologic factor in the production of diabetes mellitus (hypoinsulinism).

In July, 1925, Liu Shih-Hao and Chang Hsioo-Chien (15) reported a case of hypoglycemia, unassociated with insulin administration, blood sugar 0.075 per cent, in which the patient had symptoms similar to insulin shock. They suggested blood sugar determinations in hysterical attacks, which they thought in some cases might be due to hypoglycemia.

The First Pathologic Study of Hyperinsulinism

In April, 1927, Allan (16) reported the case of a physician, aged 40, who eighteen months before, October, 1925, began to complain of "faintness, accompanied by peculiar sensations if his meals were delayed." He recognized the similarity of his symptoms to those of an insulin reaction and had discovered that the attacks could be prevented by taking candy or food. The attacks became more frequent and more severe, with loss of consciousness and convulsions. During the attacks the blood sugar was low, less than 0.030 per cent. Operation revealed an inoperable tumor of the pancreas, with metastasis in the liver. The patient died a month later. Necropsy confirmed the surgical findings of carcinoma of the tail of the pancreas with metastatic nodules in the liver. Microscopic examination of the tumor and the nodules in the liver showed distinct resemblance to islet cells. An extract from the metastatic nodules showed insulin activity when injected into rabbits. This is the first case in which hyperinsulinism was proved pathologically. This case was later reported, with an exhaustive pathologic and clinical study of hyperinsulinism and hypoglycemia by Wilder, Allan, Power and Robertson (17).

In December, 1928, Allan (18) reported two more cases of hyperinsulinism, the second being that of a farmer, aged 52, who had suffered for two years from attacks of weakness, stupor and convulsions, with marked hypoglycemia. Diet and medicines failed to control the symptoms and operation was performed by Judd (19). The pancreas appeared normal but the tail, and a part of the body, was resected. The patient was improved by the operation, but milder attacks of hypoglycemia symptoms continued. This case seems to confirm the opinion expressed in our first report of cases. i.e., hyperinsulinism like hypoinsulinism (diabetes) may exist without demonstrable lesion of the pancreas. The third case by Allan (20) was similar to that of the second and was still under observation at the time the report was made.

Harropp (9), in August, 1927, reported the case of a diabetic aged 46, in which there was "the association of severe diabetes with extreme emaciation, inanition, diarrhoea, hypoglycemia and coma without administration of insulin." The patient's blood sugar on admission was 0.054 per cent. On unrestricted diet the blood sugar concentration arose to 0.286 per cent, but on restricted diet fell to 0.054 per cent, but with no symptoms of hypoglycemia. Five weeks later the patient suddenly went into coma and five hours before death his blood sugar fell to 0.017 per cent. The intravenous administration of dextrose failed to elicit any response or the slightest improvement. Harrop also reviewed the literature on hypoglycemia and hyperinsulinism, with an excellent discussion of the symptoms and diagnosis of hypoglycemia, with and without the administration of insulin.

Pibram (21) in 1928 reported three cases of "chronic hypoglycemia," suggesting the name "glycopenia" as descriptive of such cases. All three of Pibram's patients had low blood sugars and symptoms of weakness, chronic constipation and vomiting.

Thalheimer and Murphy (22) reported the case of a woman, aged 57, who was brought unconscious into the Milwaukee Hospital in July. 1928. For two and a half years previously about every two weeks she had been having recur-

ring attacks of somnolence, followed by restlessness and irritability. Epileptiform attacks had been noted for a year. The attacks of unconsciousness and convulsions became more frequent and more severe until in August, when they came on about three times a day, the patient dying in coma on August 18. Her blood sugar readings were low, 0.034 and 0.033 per cent. The significance of the hypoglycemia was not recognized during life, and not until the necropsy showed a small tumor, 1 by 1.5 cm., in the body of the pancreas, which proved to be a primary carcinoma of the islands of Langerhans, was the diagnosis of hyperinsulinism made.

Successful Resection of Large Portion of Pancreas for Hyperinsulinism

Finney and Finney (23) in 1928 reported the successful resection of a large portion of a normal appearing pancreas for hyperinsulinism. The case was that of a woman aged 53, referred by Drs. Sprunt and Barker, who found she had hypoglycemia with blood sugar readings as low as 0.030 per cent when fasting. The patient complained of having had, at varying intervals for four year, "spells of confusion, with mental lapses, and strange behavior." The attacks were at first slight and infrequent, growing more severe and more frequent, until they occurred almost daily. A tumor of the pancreas was suspected, but an exploratory operation revealed an almost normal appearing pancreas, and nothing abnormal was found in the abdomen. Microscopic sections of the pancreas demonstrated no pathological changes. With the hope that by reducing the number of islet cells the secretion of insulin would be decreased, two-thirds of the pancreas was resected. Blood sugar readings have been higher since the operation, but the patient has continued to have some attacks, which were thought to be psychogenic in character.

The fact that no pathological changes were found in the pancreas in this case does not prove that the islet cells were not secreting an excess of insulin, any more than that the normal appearing pancreas so frequently found at necropsies on severe diabetics does not mean that diabetes (hypoinsulinism) is not pancreatogenic. Allen's (24) experiments on partially pancreatectomized dogs showed that glycosuria and hyperglycemia does not occur until 90 per cent of the pancreas has been removed, so that two-thirds of the pancreas which the Finneys removed may not have been enough to reduce the insulin function to the point where it would not produce hypoglycemia. Since Finney has shown that the removal of three-fourths of the pancreas is a reasonably safe operation, in severe cases of hyperinsulinism, which cannot be controlled by diet, and in which an exploratory laparotomy reveals no disease, the resection of from 75 to 90 per cent of the insulin forming portion of the pancreas may offer hope of relief to the patient. Surgeons no doubt will learn from experience the amount of the pancreas to remove in cases of hyperinsulinism as they have learned that resection of the right amount of the thyroid will give relief from hyperthyroidism. It would seem safer to remove too much than too little of the pancreas for hyperinsulinism because when there is a deficiency of the secretion of insulin thus transforming the hyperinsulinism into hypoinsulinism (diabetes mellitus), a condition results that surely can be controlled by dieting and the use of insulin.

McClenahan and Norris (25) reported the case of a negro, aged 41, who for six or eight months had periodic lapses of memory, each lasting an hour or more. His blood sugar was 0.040 per cent, which suggested hyperinsulinism, and it was found that the attacks could be prevented by giving the patient food. He died of broncho-pneumonia and in spite of the intravenous administration of glucose his blood sugar remained low until death. Necropsy showed an adenoma of the pancreas, which no doubt caused overactivity of the islet calls, thus accounting for the hypoglycemia.

Hartman (26) in January, 1929, reported a case of what he called "idiopathic hypoglycemia." This case was mentioned by Jonas (8), in 1924, as having been reported by Hartman and Reimann. A man, aged 43, was admitted to the Lankenau Hospital in November, 1923, with the complaint: "If I do not eat every two hours I have a spell and lose my mind," and extreme weakness if he could not get food. The attacks usually occurred during the night. His blood sugar during an attack was 0.042 per cent. Hartman brought on an attack by withholding food, the patient complaining of weakness and difficult vision. His blood sugar was 0.052 per cent. The hypodermatic injection of 10 minims of 1:1000 adrenalin chloride solution made the patient comfortable, though the blood sugar was increased to only 0.055 per cent. No effect was obtained from pituitrin. The patient was improved by diet but later went to the state institution for epileptics, and died in 1926, presumably in a hypoglycemic attack. Hartman expressed the opinion that in this case "the excessive amount of insulin in the blood stream may have come from hyperplastic and hyperactive islands of Langerhans, from adenoma of these isles, or from carcinoma of other structures."

The First Preoperative Diagnosis of an Adenoma of the Pancreas with Cure of the Patient by Its Removal for Dysinsulinism

The first case of dysinsulinism in which the diagnosis of a probable adenoma of the pancreas was made from no other symptoms than those of hypoglycemia, and in which the patient was clinically cured by operation, was reported by Howland, Campbell, Maltby and Robinson (27) in August, 1929. The patient, a woman aged 52, who for six years had had attacks of coma and convulsions, found associated with low blood sugar levels, ranging from 0.040, 0.041, 0.045, 0.050 per cent during a twenty-four-hour study. A blood sugar tolerance test showed a diabetic curve, 0.08, 0.18, 0.25, 0.26, 0.24 per cent. Therefore, the case was considered one of dysinsulinism. In this case, in addition to the attacks of unconsciousness and convulsions, there were many minor attacks when the patient seemed dazed and became restless, or would slip down to the floor. The attacks occurred so often at the table that the authors "wondered if the smell of food was a stimulus to insulin release." An exploratory laparotomy revealed a tumor about the middle of the pancreas. It was removed with but little damage to the pancreas. No evidences of metastasis could be found. Pathological examination of the tumor showed it to be a primary carcinoma of the islands of Langerhans of the pancreas. The operation resulted in a clinical cure of the patient, the hypoglycemic attacks having stopped altogether.

Experimental Hyperinsulinism and Its Application in the Treatment of Diabetes Mellitus

DeTakats (28), in a most interesting series of experiments on dogs, in which he had induced a mild pancreatitis by a division of the pancreas by cautery, observed lower fasting blood sugar readings, and an increased carbohydrate tolerance. He believes that the evident increase in the secretion of insulin following the trauma to the pancreas resulted from hypertrophy and hyperplasia of islet tissue. He quotes Allen (29) as finding hypertrophic islets in partially pancreatectomized dogs and Mansfield (30) as having observed an increased carbohydrate tolerance in dogs following ligation of the body of the pancreas. deTakats and Wilder (31), reasoning that if division of the body of the pancreas in animals was followed by hyperplasia of islet cells and increased carbohydrate tolerance, such an operation on diabetics might stimulate insulogenesis. Consequently deTakats operated upon one of Wilder's diabetic patients, a boy of known and fixed carbohydrate tolerance and insulin dosage. The pancreas was divided by cautery close to the midline and the severed portion wrapped in omentum. Though there were complications following the operation, the boy's carbohydrate tolerance was improved, and his insulin doseage decreased. The authors state that "years of close study will be necessary to determine the end result in this case. The diabetes appears less severe than before operative intervention." Subsequently deTakats (32) operated upon another diabetic child, ligating the tail of the pancreas, with improvement in the patient's carbohydrate tolerance.

Hyperinsulinism of Functional or Nervous Origin

Hoxie and Lisherness (33) attacked the problem of hypoglycemia and hyperinsulinism by studying the records of routine blood sugar tolerance tests, and whenever low blood sugars were observed, noting the symptomology of the patients. Of 307 routine studies, 95 had a fasting blood sugar below 0.070 per

cent. In 23 cases when blood sugar was below 0.070 per cent there was sugar in the urine, suggesting the independence of blood sugar level and glycosuria. They concluded that hypoglycemia may become chronic and that it is accompanied by mental and nervous disturbances similar to that produced by acute hyperinsulinism. They believed that their cases were of functional or nervous origin, suggesting lowered sugar metabolism more than hyperinsulinism. They considered the underlying cause to be some type of exhaustion, and in their cases found that with returning strength the blood sugar returned to normal limits. In these cases the element of hypoadrenalism may have been associated with hyperinsulinism as in the cases studied by Nielson and Eggleston.

Functional Dysinsulinism Epileptiform Seizures Controlled by Dieting

Nielson and Eggleston (34), in March, 1930, reported three cases of "functional dysinsulinism seizures." Their first case, that of an unmarried woman, aged 27, who came under their observation in February, 1928, had had in three previous years eleven attacks of complete unconsciousness, and from 50 to 100 attacks of petit mal. Blood sugar readings were as low as 0.050 per cent. Without any treatment except frequent meals and suprarenal gland (6 grains every three hours, later reduced to 4-grain doses) the patient had had no attacks of either grand mal or petit mal for 22 months, and she was at her regular work when last heard from.

The second patient, a man aged 25, complained of fainting spells of five weeks' duration. His blood sugar, after a glucose tolerance test, fell to 0.069 per cent. He was given 1 cc. of 1:1,000 solution of epinephrine hypodrematically, and in ten minutes his blood sugar rose to 0.083 per cent. He was ordered to eat between meals and was given three tablets (6 grains) suprarenal gland by mouth; and, with no other treatment, the patient had had no hypoglycemic attacks in seven weeks.

The third patient, a man aged 23, had suffered 125 to 150 attacks of grand mal in 13 years. All but three had occurred before breakfast. He also had had innumerable attacks of petit mal. He was taking 3 grains of phenobarbital daily. After a glucose tolerance test a low blood sugar, 0.064 per cent, was obtained. The patient was given a glass of orange juice at 6 A.M. and though his phenobarbital was reduced to 1 grain a day, he had had no attacks in eighteen months. Neilson and Eggleston tried frequent feedings and suprarenal gland in cases of idiopathic epilepsy without any beneficial effect.

Obesity, Hyperinsulinism and Diabetes

Winans (35) in November, 1929, reported three patients having symptoms associated with hypoglycemia in whom he thought he could exclude any other endocrine disturbance except an excessive secretion of insulin by the islet cells of the pancreas. All three of Winans' cases gave a history of having lived on a high carbohydrate diet, which he thought was the exciting cause of the hyperinsulinism, with the resulting hypoglycemia. The important symptoms of the first case were severe headaches and inability to concentrate about 4:00 P.M. His blood sugar was low during an attack, 0.073 per cent. The complaint of the second patient, an obese woman, was weakness, trembling and inability to keep from crying. She had been dieting to reduce. Her blood sugar during an attack was 0.059 per cent. The third patient, an overweight woman, aged 30, complained before lunch and in the middle of the afternoon of attacks of weakness, dizziness, pain in "the pit of her stomach," and extreme hunger. Her blood sugar late in the afternoon was 0.067 per cent. Winans said that his patients "did best on a balanced diet and with regular systematic exercise." He concludes by saying: "Obesity, presumably from overeating, precedes diabetes. As long as the pancreas can respond to the overstimulation of excess diet, they (the obese) are in the class of hypoglycemia (hyperinsulinism), whereas if the pancreas fails, they progress to diabetes (hypoinsulinism)."

Tachycardia, Dyspnoea and Headaches Associated with Hypoglycemia

Waters (36) reported three cases of spontaneous hypoglycemia, which were relieved by a low carbohydrate, high fat diet, with frequent feedings. The symptoms were quite different in all of them. The first patient, a woman aged 54, had paroxysmal attacks of tachycardia, occurring three or four hours after meals, often accompanied by weakness, hunger, nervousness, and a sense of suffocation. The blood sugar during a seizure was 0.060 per cent, when fasting 0.066 per cent, and three hours after a 50-gram carbohydrate meal was 0.070 per cent. The paroxysmal tachycardia and the hypoglycemic symptoms were

relieved on a moderate carbohydrate high fat diet, and two-grain enteric coated tablets of suprarenal substance.

The second patient, a woman, aged 45, complained of attacks of dyspnoea, weakness, profuse sweating, usually coming on three or four hours after meals, and relieved by taking food. The blood sugar in an attack was 0.051 per cent. Almost immediate relief was obtained by hypodermatic administration of epinephrin. This patient likewise was relieved by a low carbohydrate, high fat diet, and three weeks later her blood sugar three hours after breakfast was 0.075 per cent.

The third patient, a man, aged 48, had attacks of generalized headaches, accompanied by hunger, sweating, weakness and a sense of suffocation. His blood sugar during an attack was 0.061 per cent. He was relieved by a low carbohydrate, high fat diet, and three weeks later his blood sugar three hours after breakfast was 0.075 per cent.

In the discussion on Walter's paper, Sprunt (37) reported two severe cases of hypoglycemia, associated with "very bizarre nervous phenomena, exactly like those observed in diabetics after an overdose of insulin."

Sexton (38) mentioned two cases presenting low blood sugars and symptoms similar to insulin "shock." In one patient, a girl, who had syncopal attacks, diagnosed as petit mal, with a blood sugar of 0.060 per cent, was placed on a ketogenic diet with marked improvement in the frequency of the attacks.

Hypoglycemic Attacks Associated with Adenoma of Suprarenal Gland

Anderson (39), in 1930, reported the case of a man, aged 33, who felt well on retiring but the following morning was found in a semi-conscious state in which he remained for twelve hours. He then became normal and remained so for two days, when he became drowsy and slightly delirious. He was given glucose intravenously and in half an hour became conscious and was given orange juice and glucose twice by mouth. He seemed improved when about 2 A.M. on the morning of the fourth day he became unconscious and had a convulsion. His blood sugar was 0.060 per cent. Three hundred cc. of 20 per cent glucose was given intravenously, which was followed by immediate improvement. He was then given carbohydrates freely and at frequent intervals, making a rapid convalescence. He remained well for two months, then became unconscious and remained so for several hours. Two days later he had another attack, and though he was given glucose freely and adrenalin in doses of 1 cc. of a 1/1000 solution several times, he died five days later. The lowest blood sugar observed was 0.040 per cent. Necropsy revealed a tumor of the left adrenal gland. "The pancreas showed a definite increase in vascularity, especially that of the tail." The tumor was diagnosed as carcinoma of the cortex of the adrenal gland by Dr. Shields Warren who, in his comments, said: "Certain tumors contain large amounts of glycogen, and are also known to produce either insulin or a substance very similar to it. This substance produced by tumors goes by the name of insulinoid in the literature on the subject. Certain of the experimental rat tumors are known to produce considerable amounts of insulin-like substance." Anderson does not attempt to explain the relationship of the adrenal tumor to the hypoglycemia, but suggests the interdependence of the functions of the islet cells of the pancreas and the adrenals.

Hyperinsulinism Attacks Due to Adenoma of Pancreas Cured by Operation

Carr, Parker, Grave and Fisher (40), in April, 1931, reported the case of a boy aged 19, who had recurring periods of unconsciousness, accompanied by profuse perspiration, slight cyanosis and at times varying muscular movements. Spontaneous recovery would take place after a few hours when the patient would be ravenously hungry, and after eating he would be perfectly normal. A diagnosis of epilepsy had been made before he was admitted to the hospital. A tentative diagnosis of spontaneous hypoglycemia due to hyperinsulinism was made. His blood sugar during at attack was 0.044 per cent. A dextrose tolerance test showed blood sugar values ranging from 0.081 per cent, 0.061 first hour; 0.062, three hours; 0.042, eight hours, to 0.054 per cent in twelve hours. He was much improved for four months by dieting with frequent meals, when the attacks became more frequent and more severe. Though the patient was quite young for a pancreatic tumor, an exploratory laparotomy was advised and performed on October 22, 1930. A tumor about 2 cm. in diameter was found in the upper posterior border of the pancreas at about its mid-portion. It was removed and found to be a B-cell adenoma. The patient recovered promptly from the operation and has had no more of the hypoglycemic attacks. A dex-

trose tolerance test three weeks after the operation approximated the normal as follows: fasting, 0.096 per cent. In one hour after taking 155 gms. dextrose and the juice of three oranges, his blood sugar was 0.168; in two hours, 0.122; in three hours, 0.085; in five hours, 0.096 per cent. The brilliant result of the operation surely justified the exploration.

The Futility of Giving Glucose Solutions Per Rectum

Schmidt and Cary (41), in a study of 33 cases of non-diabetics, shortly before death found that 12 or 36 per cent showed low blood sugar readings, from 0.028 to 0.075 per cent, before death. They considered hyperinsulinism with excessive utilization of sugar, or hepatic insufficiency, as among the possible causes, though they did not offer any positive explanation of the phenomena. Several of the cases were post operative hypoglycemia, for which they offered no explanation. Three of the cases of post operative hypoglycemia were receiving a Murphy Drip of 5 per cent dextrose, showing the futility of that method of administering soluble carbohydrates per rectum. They cited Pressman's (42) work, which seemed to prove that following the introduction of dextrose into the rectum, the blood sugar falls without a preliminary rise, and that hypoglycemia would be exaggerated rather than improved by the administration of sugar via the rectal route.

Hyperinsulinism with Hypertrophy of Islands of Langerhans

That there may be a pathological basis for an excessive secretion of insulin seems proved by the case Phillips (43) reported in 1931. A negro, aged 56, was found in the street unconscious. He had complained before of marked frequency of urination. His blood urea nitrogen was 133 mgm., and blood sugar 0.045 per cent. He remained unconscious and two days later his urea nitrogen was 203 mgm. and creatanin 19.2 mgm. and blood sugar 0.025 per cent. He died a few hours later. Necropsy showed subacute glomerular nephritis, which accounted for the very high urea nitrogen and creatinin. The pancreas was practically normal except for a definite hyperplasia of the islet cells. The average size of the islet cells was at least 50 per cent higher than normal. Phillips concluded that the hypertrophy of the islands of Langerhans with increased insulin production was the etiologic factor of the hypoglycemia in this case. He concluded that high sugar ingestion may provoke hypertrophy of the islands and bring about chronic hyperinsulinism. Phillips cites a case reported by Dubreuil and Anderodias (44) of giant islands of Langerhans in a child born of a diabetic mother. The islands were from twenty to thirty times larger than the normal. Phillips also cites a case reported by Gray and Feemster (44) of "compensatory hypertrophy and hyperplasia of the islands of Langerhans in the pancreas of a child born of a diabetic mother." The premature child died on the third day of life and on that day its blood sugar was 0.067 per cent. The hyperplasia of the islet cells was considered by the author as compensatory to the increased blood sugar of the mother.

Hyperinsulinism Attacks Before and During Menstruation

A most thorough study of a case of hyperinsulinism has been made by Dr. Clarence Weil of Montgomery, Alabama, from January to May, 1931. The writer had the privilege of seeing this patient with Dr. Weil, and with his permission a resumé of the important features of the case is included in the brief discussion of the cases of hyperinsulinism found in medical literature. Weil will publish his complete report soon. A woman, aged 29, had recurring attacks of unconsciousness and convulsions for three months, occurring in the early morning hours and at other times several hours after meals. The attacks came on before or during the menstrual period. A glucose tolerance test showed very low sugar concentrations in the blood, i.e., fasting 0.057 per cent. She was then given 100 gm. glucose, and a half hour later her blood sugar was 0.069; one hour later, 0.074; two hours later, 0.065. The lowest blood sugar was 0.037 per cent, but one test failed to show any change in color.

Weil tried a high carbohydrate diet, but found that it was followed by lower blood sugar readings a few hours after meals, and with recurrences of the periods of unconsciousness and convulsions. He then tried a relatively low carbohydrate, high fat diet, with frequent feedings, one at 4 A.M., with the result that though no medicines have been given the convulsions have been less frequent, and her blood sugar readings became somewhat higher, as follows: 0.050, 0.040, 0.050, 0.068 and 0.082 per cent. The symptons in Dr. Weil's case were so similar to those in the cases by Allen, Wilder, et al., Howland Campbell, et al.,

and Carr, Parker, et al., in which neoplasms of the pancreas were found, that an exploratory laparotomy has been considered.

Hyperinsulinism and "Nerves"

Gammon and Tenery (46) report a case diagnosed as "nerves" by several physicians, but they proved the attacks to be due to hyperinsulinism and cured the patient by frequent feedings with a high carbohydrate diet. A woman, aged 39, in 1926 had had three attacks each month of weakness, unconsciousness and muscular twitchings. Then for two years she had had no attacks. Then they recurred at weekly intervals for five or six weeks. She then discovered that the attacks could be prevented by augmented diet. They recurred, however, in a few months, the attacks then coming on daily. In addition to the severe seizures she had milder attacks before the noon or evening meal, of irritability, weakness, perspiration, a tendency to mix words and drowsiness, followed by sleep, unless food was taken. Her fasting blood sugar was 0.050 per cent. A sugar tolerance test showed blood sugars as follows: Fasting, 0.050, in 45 minutes 0.225; 2 hours, 0.225 per cent, a diabetic curve but with no sugar in her urine. The authors suggested the term "dysinsulinosis" as descriptive of the condition. The patient was completely relieved on a high carbohydrate diet, with feedings between meals and at bedtime. A year later her fasting blood sugar was still low, 0.047, but there was marked improvement in her blood sugar curve after a glucose tolerance test; 45 minutes, 0.0145 per cent; one hour and 45 minutes, 0.125 per cent, and 2 hours and 45 minutes, 0.111 per cent. Gammon and Tenery present a comprehensive discussion on the general subject of hypoglycemia, with an excellent review of the literature on that subject.

CONCLUSIONS

A review of the literature on hyperinsulinism and dysinsulinism with reports of about fifty cases, including thorough studies of the symptoms, laboratory and necropsy findings by a number of able clinicians and pathologists, seems to justify the following conclusions:

1. It has been proved definitely that lesions of the pancreas may cause hypersecretion of insulin, thus producing hypoglycemia, with identical symptoms to those induced by overdoses of insulin. Therefore, it may be stated positively that a new disease has been discovered, one with a definite symptom syndrome, that usually is amenable to treatment, the mild cases by dieting, and the severe cases, particularly those associated with tumors of the pancreas, may be cured surgically.

2. Hypoglycemia may result from a number of causes, *i. e.*, (a) hypersecretion of the islands of Langerhans of the pancreas; (b) deficient glycogenesis in the liver, either from poisons as arsephenamin or other arsenicals, phenylhydrazine, and other toxic substances, or from massive tumor of the liver; or (c) hypofunction of the adrenals, thus interfering with glycogen lability; (d) ovarian dysfunction; (e) pituitary dysfunction. Hypoglycemia, therefore, is a condition of the blood—not a disease—resulting from dysfunction of any one of several organs of internal secretion.

3. According to modern nomenclature the disease entity due to the excessive secretion of insulin should be called hyperinsulinism. Hypoglycemia bears the same relation to hyperinsulinism that hyperglycemia bears to hypoinsulinism (diabetes mellitus). No one would think of reporting a case of diabetes mellitus (hypoinsulinism) as hyperglycemia. Hypoglycemia should be employed in the report of cases as a qualifying word, and not as a disease, just as hyperglycemia, which causes definite symp-

toms, i. e., polyuria, polydipsia, polyphagia, etc., is used in connection with diabetes mellitus. The Quarterly Cumulative Index Medicus very properly lists hypoglycemia under the heading of blood sugar, and it places hyperinsulinism under diseases of the pancreas.

4. Judging from the number of recent cases of hyperinsulinism reported, and the study of fasting blood sugars in our series of 1497 non-diabetics showing hyperglycemia in 51 and hypoglycemia in 67 it seems probable that hyperinsulinism occurs almost as frequently as hypoinsulinism (diabetes); and that careful history taking, routine fasting blood sugars, glucose tolerance tests, and blood sugar studies at the time of unexplained nervous attacks, periods of unconsciousness, and convulsions, will prove many of them to be associated with insulogenic hypoglycemia. Since a number of cases of hyperinsulinism have been diagnosed erroneously as epilepsy, every case of grand mal, and petit mal, should have fasting blood sugar determinations, glucose tolerance tests, and blood sugar studies during, or as soon after the attack as possible, in order to exclude hyperinsulinism before making a positive diagnosis of epilepsy.

5. A relatively low carbohydrate, moderate protein and high fat diet, with food every two or three hours during the day, and at night, if necessary to prevent nocturnal attacks, will give relief from symptoms in most cases of hyperinsulinism; but the dieting may have to be continued permanently as in the treatment of diabetes, to get lasting results. Epinephrin, or adrenalin chloride, 1 to 1000 solution in 0.5 to 1 cc. (7 to 15 minim) doses hypodermatically, will often restore consciousness in hypoglycemic coma. Dextrose intravenously in 10 to 25 per cent solutions given slowly; and subcutaneously, in 5 per cent solutions, are indicated in hyperinsulinism with unconsciousness. It seems proved that glucose or dextrose per rectum, either by Murphy drip or by small enemata, is not absorbed, and therefore is of no value. Surgery offers hope for relief in the severe cases of hyperinsulinism when dieting and medical treatment fails.

6. It seems probable that one of the causes of hyperinsulinism is the excessive ingestion of glucose-forming foods; and that, as the result of overactivity induced by the overeating of carbohydrates, the islands of Langerhans become exhausted and hypoinsulinism (diabetes) follows. It is possible that the hunger incident to hyperinsulinism may be a cause of overeating and, therefore, the obesity that so often precedes diabetes.

7. Since hyperinsulinism has been produced experimentally in animals, it seems probable that it, like hypoinsulinism (diabetes mellitus) may follow infection, or trauma, of the pancreas. Adenoma and carcinomata of the body of the pancreas has been proved to be a cause of the severe forms of hyperinsulinism.

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CORTIN IN ADDISON'S DISEASE*

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This completes the observations on a case reported earlier in this Journal (1). So far as we know it is the first case with practically complete adrenal cortical insufficiency treated with cortin.

After remaining in the hospital for 97 days the patient was allowed to go home. He injected himself four times daily with cortin. He felt well, slept soundly and had a good appetite. On the eleventh day at home the amount of cortin was reduced one-half. Three days later in the morning after eating breakfast he felt very ill, vomited many times, but felt no pain except in the epigastric region. He became very thirsty, was unable to talk very well and finally "everything was blank" according to his statement. He returned by ambulance to the hospital. He was given cortin every two hours subcutaneously (the product of 300 gm. of cortex) for twenty-four hours; then the interval was gradually increased and the dose decreased until on the fifth day after readmission the cortin per day was the standard minimum for him (1200 gm. cortex). He made a good recovery, being allowed to return to his home 17 days after readmission to the hospital.

The number of injections per day was reduced to three while the amount of cortin was increased fifty per cent, but he did not fare so well as with the original minimal dosage (1200 gm. cortex) divided into four injections per day.

The basal metabolism was determined from time to time, always being less than normal.

During the first five months after testing for the fatigue point had been started (25 days after his first admission) there was very little change in the ability to do work without fatigue. Likewise the appetite and body weight had changed little, the latter being 105-110 lb.

Six months after the first admission the patient returned to the hospital for observation. During the next month the appetite increased, there was a gain of 10 lb. in body weight and a constant systolic blood pressure of 90-95 mm. Hg. Pigmentation had increased. The patient was up three to four hours a day. His ability to do work without fatigue increased so that 199 days after first admission he could do six times as much work on the ergometer without fatigue as at any time during the first five months. He could walk quite fast and felt much better. At this time a mild respiratory infection developed. Two days later his temperature was

*This study was aided by a grant from the National Research Council.

101.5°F. Later a pain developed over his right scapula. This disappeared but was followed by a chill, nausea and vomiting. The temperature rose finally to 105°F. and the leucocyte count to 30,000. In spite of a large increase in cortin he died of pneumonia 238 days after his first admission to the hospital.

The pathological findings in this case reported by Terplan and Sanes* have considerable significance. The adrenal cortices were almost completely absent while the medullae were almost normal. The chrome reaction indicated no epinephrin insufficiency. Therefore, the low blood pressure 90-95 mm. was probably due to a cortical rather than a medullary insufficiency.

The presence of well stained normal medulla coupled with almost complete absence of cortex indicated that cortex was unnecessary for the formation of epinephrin. This seems to disprove the theory that the precursors of epinephrin are found in the cortex (2).

*See page 69, this issue.

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OVARIAN THERAPY*

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For several years ovarian therapy has been in a state of flux due to broadening of our concept of the physiological function of the ovary and to the discovery, isolation and purification of definite chemical substances produced by the ovary. The older miscellaneous ovarian extracts have been replaced by standardized products, the activity of which has been fully demonstrated in lower animals, and to a lesser degree in man. Up to the present time the clearcut striking results obtained in animals have not been reproduced in human subjects. There is, however, much hope for future human therapy.

There are two outstanding reasons why results of animal experimentation cannot be used as criteria for human therapy, viz., differences in sexual cycles between man and other animals, and psychological factors.

Oestrus marks the height of the cycle, characterized by ovulation, mating activity, and growth of genital organs. Menstruation is associated with growth of the uterus, but it is not synchronous with ovulation, nor is the human inclination to mate limited to this time. In spite of the fact that menstruation and oestrus are not similar, irregularity in rhythm and variation in amount of menstruation is the best symptom indicator for disturbances of the human sexual cycle.

Psychological factors are unimportant in animal experimentation, but they play an important role in many functions of the human body and therefore must be excluded before the efficacy of any therapeutic agent administered to the human being can be fairly judged.

A logical basis for ovarian therapy was established at the beginning of the present century when Knauer (1) demonstrated that ovarian transplants substituted satisfactorily for normal ovarian function. His work proved conclusively that the stimulus from the ovary to other portions of the genital tract was hormonal. The next advance was due to Prenant (2) and Fraenkel (3), who independently showed the effects on the sexual cycle when the corpus luteum was disturbed. Importance was attached to this demonstration to the extent that dried extracts of the ovary came into wide use. Probably to this day these dried extracts retain the lead in popularity among physicians for treatment of menstrual disorders. But no one has yet demonstrated conclusively that such therapy has any specific effect. However, medical literature during the last twenty-five years contains numerous accounts of striking results obtained by the use of corpus luteum extract,

*Read before the Division of Medical Chemistry, American Chemical Society, Buffalo, Sept. 3, 1931.

ovarian residue and whole ovary. In the light of our present knowledge these apparently satisfactory results can be explained either by coincidence or psychic effect.

All this confusion concerning oestrus and menstruation, together with the supposed therapeutic results obtained by administration of extracts, emphasizes the difficulty which arises when one attempts to translate the results of animal experimentation into the terms of human therapy. If oestrus of animals and human menstruation were synonomous, the problem of correlation of results would be a relatively simple matter. But, with the exception of monkeys, other animals do not menstruate. Then, too, the conditions for animal experiment can be controlled, while in human therapy many extraneous factors need to be evaluated. This is especially true of psychic influences.

In spite of the fact that the older dried preparations of the ovary have been accredited with some brilliant clinical results, no one has been able to influence the sexual cycle of animals with these preparations. This fact alone discredits the possible efficiency of these preparations in the human subject. More careful check of these preparations has shown that when all psychic influences are removed and other preparations, similar in character, not derived from ovaries, are substituted for the ovarian preparations, equally good results have been obtained. It must be admitted, however, that when a patient is aware that there is such an ovarian deficiency as occurs following removal of these organs at operation or during natural menopause, the psychic suggestion that the deficiency may be supplied by an ovarian preparation is frequently beneficial. Inasmuch as many of the symptoms of the menopause are psychic it is a justifiable procedure to continue the use of these ovarian extracts as a psychotherapeutic measure, because the same relief is not experienced if the patient's mental attitude towards the ovarian deficiency is not considered.

It is generally conceded that there are clinical evidences of ovarian deficiency manifested by disturbances of menstruation and by structural body changes, so well described by Rowe (4). There is not, however, the same consensus of opinion concerning manifestations of hyperactivity of the ovaries, for many do not believe that the latter condition exists. Until more convincing proof of hyperfunction is adduced, treatment of such a condition cannot have a logical basis. But, for correction of hypofunction, two lines of attack are open either to supply the deficiency or stimulate the ovary to greater activity.

Products of the ovary have not been shown to have any stimulating effect on that organ. They merely supply a deficiency. But, the luteinizing hormone of the anterior lobe of the hypophysis can be shown to have a direct effect on the ovary.

Although such preparations derived from the ovary as progestin, relaxin, corporin, vasculin, etc., exert a specific influence in animals, they are not yet available for clinical use. Theelin and theelol are now prepared

satisfactorily for human therapy. While it has been assumed that theelin is the active principle of such commercial preparations as estrogen, amniotin, folliculin, oestrin, progynon, etc., it is quite possible that theelin and theelol have been present together. The combination of the two may explain the discrepancies in results obtained by various observers. Inasmuch as our results have been similar with theelin, estrogen, and amniotin, we assume that before theelin was available we were using a similar product.

METHODS OF ADMINISTRATION

Inasmuch as animal experiments were carried on by injection of ovarian follicular hormone, it would be logical to use the same method for human therapy. However, the difficulty of obtaining cooperation of patients to the extent that they would come for frequent injections was sufficient to interfere with satisfactory clinical use. Also, with the earlier preparations it was found difficult to obviate local reaction about the site of injection. While a few of the earlier workers with these potent products claimed results by oral administration, there was great discrepancy in the dosage required, and for the most part the results were negative. The difficulty of the injection method and the unsatisfactory results from the oral method lead us to seek for another form of administration.

Inasmuch as under natural conditions the hormone is being secreted more or less continuously by the ovary, it seemed desirable to simulate this condition as nearly as possible. We [Pratt and Smeltzer (5)] found that ovarian follicular hormone is absorbed through the nasal mucous membrane, and therefore induced the patients to apply this substance by means of a nasal spray. It has been found that it is absorbed readily through the mucous membrane and results obtained by this method have been equally as good as by injections. Furthermore, it is a method which the patients may use at home, obviating the necessity of frequent visits to the office. The difficulty encountered with the nasal spray was the necessity of frequent applications. It could not be carried around by those who were employed, therefore it was useful only to those at home.

Nasal jelly was tried, but two difficulties were encountered. First, an ideal vehicle which was free from after effects was not found. Second, the hormone was not given up uniformly from the vehicle. However, definite results have been obtained with nasal jelly.

Vaginal suppositories offer another method of administration, which in many instances is quite valuable. The absorption from the vaginal mucous membrane has been demonstrated beyond doubt, but the chief difficulty encountered is that in many instances the vehicle containing the hormone is not retained within the vagina, so that a greater part of the product is lost. It is interesting to note the mental effect, because many patients feel that inasmuch as their problem is one of the genital tract that local applicaion is much more effective because, in general, the nature of hormone acting through the blood is not well understood.

INDICATIONS FOR USE AND RESULTS OBTAINED

Even though oestrus and menstruation are so different, it would seem that clinically the best symptom indicator of abnormality of the sexual cycle is a disturbance of menstruation. Some of the conditions for which ovarian therapy has been considered necessary are: Menopause, secondary amenorrhoea, scanty and infrequent menstruation, dysmenorrhoea, sterility, primary amenorrhoea, menorrhagia, metrorrhagia, and frigidity.

Menopause: Many claims have been made for the efficacy of ovarian hormone in treatment of both the artificial and natural menopause. Our first personal experience seemed to justify these claims. However, by carefully excluding the psychic factors, equally good results have been obtained by other preparations not related to glands of internal secretion. It was thought that perhaps this was due to insufficient dosage, so as much as twelve hundred rat units of theelin have been administered in a period of three days without any appreciable effect being noted by the patient. This has been done both with and without the patient's knowledge of what she was getting. Inasmuch as so many of the symptoms of the menopause are on a nervous basis, it is our impression that, up to the present, specific ovarian hormone therapy is unsatisfactory except as a psychotherapeutic agent.

Secondary Amenorrhoea: This term is meant to include amenorrhoea in all those individuals who start menstruation at a normal age but later cease to menstruate, or their menstruation becomes scanty and irregular in rhythm. It is in this group that the most satisfactory results have been obtained. This type of amenorrhoea would seem to indicate a real deficiency of ovarian internal secretion which could be supplied by introducing the hormones into the body. Inasmuch as there is no way of measuring the amount of deficiency, the necessary dosage is uncertain. However, it would seem obvious that in some instances the deficiency would be so slight that even a small dose would make up the loss, while in others even a large dose would be inefficient. This assumption corresponds with the clinical results. Some patients in whom all extraneous factors have been removed have been followed carefully over a period of a few years, and they have responded well to this form of therapy. We feel, in certain instances at least, that definite results may be obtained. In this group, reports of a single menstruation following therapy should be excluded as inconclusive. Such a menstruation is more probably a coincidence.

Primary Amenorrhoea: Primary amenorrhoea includes disturbances in those individuals who have gone well past the age at which menstruation should normally begin. In no instance have we noted a satisfactory result of specific ovarian hormone therapy in this group.

Menorrhagia: The increased amount of flow at the time of menstruation might be looked upon as a result of hyperactivity of ovarian function. However, there is considerable difference of opinion as to whether there is

such a thing as "hyperovarianism." If the ovary is hyperactive one would not expect administration of theelin to decrease the amount of flow; however, in several instances the duration and amount of flow have been diminished, apparently due to theelin. The theoretical explanation of this is too complicated to consider at this time.

Metrorrhagia: There are some claims in the literature as to the effectiveness of ovarian treatment of metrorrhagia. Our own personal experience has been uniformly unsatisfactory.

Dysmenorrhoea: Inasmuch as dysmenorrhoea has been so frequently reported as improved by all sorts of therapy, it is not surprising that there have been claims for relief of this condition by some of the ovarian hormones. It would seem that most of these are unjustified. Aside from the small percentage of dysmenorrhoeas which are on a mechanical basis and can be relieved by correcting the mechanical disturbance, most such complaints are largely psychic and can best be treated by proper psychotherapeutic measures. At the present time there seems to be no justification for ovarian hormone for this condition.

Frigidity: Many claims have been made for the successful use of ovarian preparations of all sorts to overcome frigidity. This again is largely a psychic condition in individuals who have attained normal development. Where infantilism is associated with frigidity there is no evidence that ovaran preparations stimulate growth of infantile organs. Proper therapy should be directed toward stimulating the ovaries.

Sterility: Several claims have been made for the efficacy of ovarian therapy in cases of sterility. Personal observation of a few of these might lead to the conclusion that such treatment is effective. However, we cannot help but feel that results obtained are coincidental, because if a number of sterile patients are followed for considerable period of time it is found that, without the use of any particular therapeutic measures, sterility is finally overcome. Inasmuch as relative sterility may exist for as long as twenty years, it seems unsafe to conclude that any therapy is effective in overcoming it. This is a subject for controlled study, however, with rigid statistical analysis of results. It is quite possible that some change in the acidity of the vaginal secretion may be effected by such therapy.

So far the discussion has been confined to hormones of the ovary. Although a satisfactory specific hormone in the ovary is to be desired it must be admitted at the present time that more satisfactory results have been accomplished by administration of thyroid derivatives than by any of the ovarian preparations. The fact of the dependence of the ovary upon the thyroid is well demonstrated clinically. The theory as to the manner in which it acts is a matter of discussion. A great deal is said about the interrelation and the balance of the glands of internal secretion. It would seem that a simple explanation would be that when the thyroid functions normally the hormone is secreted in the blood almost continuously. It is carried by the blood to all parts of the body and may be used by any

tissue or organ which has the ability to withdraw it from the blood stream. Unquestionably, a certain amount of this thyroid hormone is necessary, directly or indirectly, for normal function of the ovary. It can be readily understood that if the thyroid hormone is below normal that the function of the ovary might be below normal, and bringing the thyroid to its normal level would have a similar effect on the ovary. The dependence of the ovary upon the thyroid is so striking that in all clinical treatment of ovarian deficiency it seems important first to stabilize the individual on thyroid. This should be done over a long enough period so that it can be determined whether or not the condition treated is due purely to thyroid deficiency before any specific ovarian therapy is begun.

One of our patients, previously reported, illustrates this interrelation very strikingly. She has been followed for several years, and when receiving both thyroid extract and theelin has menstruated regularly, but if either one of these agents is omitted menstruation becomes scant and very irregular.

Luteinizing hormone of the anterior lobe of the pituitary has also been demonstrated to be an important factor in influencing the function of the ovary. The use of this is still too limited to draw many conclusions. There is one condition, however, in which it has been of the greatest clinical value. There is a condition known as cystic hypertrophy of the endometrium, in which the lining of the uterus grows to great height and contains numerous small macroscopic or microscopic cysts. This overgrowth is accompanied by more or less continuous and excessive bleeding. Is occurs during the early and late ages of menstruation. The bleeding is sometimes so excessive that the patient becomes anemic and may be confined to bed from weakness. There are a number of instances in which bleeding has stopped in a very short time, even a few hours after the first injection of anterior lobe luteinizing hormone. Novak (6) recently reported 51 such cases. The results are very striking and are fairly uniform.

Such extraneous factors as influence of the thyroid and psychic influences have been mentioned. Also, coincidences must be included as an explanation for many apparent results. In addition to these there may be changes in conditions of living such as from a state of confinement to one of outdoor exercise; change of diet and habits of rest and relaxation. Quite frequently when the symptoms trouble the patients sufficiently to seek relief their general attention is focused on their manner of living, and, with or without the directions of a physician, many factors may be changed. It is essential that all these factors be fully considered before any conclusions are drawn concerning a specific therapy.

Only one definite result from the use of theelin has been consistently demonstrated, *i.e.*, growth of the uterus. The amount and rate of growth may vary with different individuals and in the same individual, for there is probably considerable variation in the amount of ovarian deficiency encountered.

The control of bleeding in hemophiliacs by administration of ovarian extract and transplant, as recently advocated by Birch (7) is most interesting. He suggests two possible explanations for the fact that a disease limited to the male sex is transmitted only through the unaffected female. Either the presence of male sex organs or inhibition by the female sex organs is necessary. His observations on two cases tend to support the latter explanation. Since hemophilia is not a common condition, it will not be easy to arrive at a final decision as to possibility of ovarian therapy.

SUMMARY

1. Definite clinical results have been obtained by the use of theelin, but the frequency with which success occurs is disappointing.

2. Evidence of increase in size of uterus and response to administration of theelin has been demonstrated.

3. Secondary amenorrhoea has been satisfactorily treated with theelin.

4. Thyroid therapy frequently corrects scanty and irregular menstruation.

5. Bleeding in cystic hypertrophy of the endometrium is checked by luteinizing hormone of the anterior lobe of the pituitary.

6. Claims for efficacy of ovarian extract, whole ovary, and ovarian residue may be explained as coincidence and psychotherapy.

7. Progestin, relaxin, corporin, and vasculin have not been available for clinical use.

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CLIMATE AS A POTENTIAL FACTOR IN THE ETIOLOGY OF EXOPHTHALMIC GOITER AND THE OTHER METABOLIC DISEASES

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Intensive studies of the past several decades as to the basic cause for exophthalmic goiter have not been very successful. The use of animal experimentation and study of individual patients have yielded considerable knowledge of the disease, but very little insight into its etiology. There remains, however, another avenue of approach to the problem, an avenue not exhaustively used thus far. This new method of attack consists, not in any form of animal work or individual case study, but in viewing the disease in its broader biological aspects, determining where it is most prevalent and most severe in the human race as a whole, and then attempting to find the specific factors of those localities which might act as etiological agents.

In such an attack on the problem it is also important that the study be not restricted to exophthalmic goiter alone but be made to include dysfunction of the other endocrine glands closely related to the thyroid. Such diseases as diabetes, Addison's disease and pernicious anemia—diseases of endocrine or metabolic exhaustion—might exhibit much the same incidence as exophthalmic goiter and thus lend added value to the study.

I have been engaged upon such a study as this for the past three years. The results, which I shall set forth in this article, have proven most interesting and instructive. They seem definitely to indicate that there exists an important climatic factor in the causation of the exophthalmic goiter and the other metabolic diseases.

In studying the disease distribution it was felt that the mortality statistics would be the most complete and most reliable that could be obtained. No figures are available as to the actual incidence of such disease in the living population. Mortality statistics from the Registration Areas of the United States and Canada were used. Deaths from each disease was calculated as percentage of the total number of deaths in order to show the relative importance of the disease among all causes of death.

Map I presents the death rate from exophthalmic goiter over the continent of North America. Certain important points stand out clearly. Two areas of high death rate are seen, one centering around the Great Lakes area and the other on the Pacific Coast. The entire South possesses a low rate, as does a narrow strip of territory up along the Atlantic Coast. And, finally the rate is seen to decline farther toward the north just as it does toward the South. This map should be compared closely with the

later maps for diabetes and pernicious anemia, and with the ones showing storm frequency and temperature variability.

The exophthalmic goiter death rate in the United States was steadily rising up to 1926, but has been falling since then in all areas except that around the Great Lakes and out toward Kansas. This is true in the high rate area of the Pacific Coast. Around the Great Lakes and out toward Iowa and Kansas, however, the rate continued its alarming increase for another year or two. The following figures of the death rate from exophthalmic goiter per 100,000 estimated population show these facts:

DEATH RATE FROM EXOPHTHALMIC GOITER IN THE REGISTRATION AREA OF CONTINENTAL UNITED STATES AND OF SELECTED STATES

Year	Death Rate	Year	Death Rate	Year	Death Rate	Year	Death Rate
1910	1.3	1915	1.6	1920	1.9	1925	3.4
1911	1.3	1916	1.6	1921	1.7	1926	5.0
1912	1.5	1917	1.7	1922	2.0	1927	3.9
1913	1.5	1918	1.7	1923	2.1	1928	3.6
1914	1.5	1919	1.8	1924	2.8		

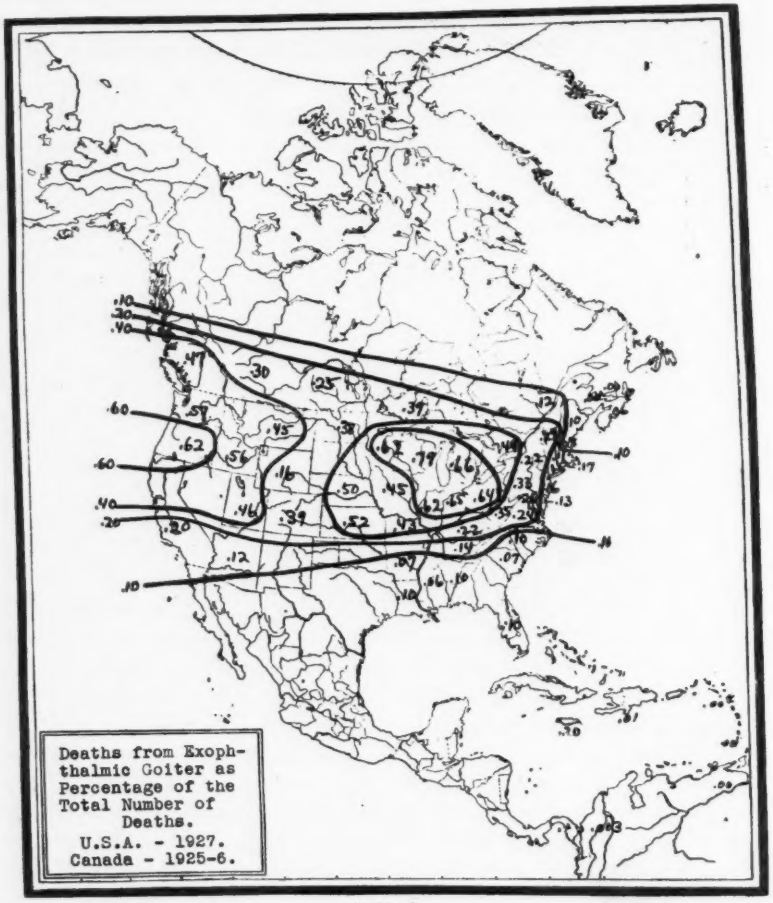
Year	Illinois Death Rate	Wisconsin Death Rate	Kansas Death Rate	Iowa Death Rate
1919	2.9	2.3	1.4	...
1920	2.8	3.1	2.1	...
1924	4.2	5.2	2.7	2.8
1925	5.7	5.1	4.1	3.8
1926	6.6	6.3	3.9	4.9
1927	7.1	8.1	5.3	4.6
1928	7.1	8.0	5.2	5.0

Turning now to the other metabolic diseases, we see that the death rate from pernicious anemia (Map II) shows geographic variations almost identical with those for exophthalmic goiter. The same high rate area is found centering around the Great Lakes area, with the severity of the disease diminishing toward both the North and the South. Like exophthalmic goiter, pernicious anemia showed a rapidly increasing death rate up to 1926, but since then the rate has been declining. This was attributed to the widespread use of liver feeding and liver extracts from 1926 on, but the coincidence in the time of this decline in rate with that for exophthalmic goiter raises an interesting question for later discussion.

Map III shows much the same geographic differences in the diabetes death rate as were seen for the other two diseases. These differences are not due to differences in the composition of the population, for adjusted rates show the same picture, although to a slightly less marked degree. To emphasize this point, I have calculated the death rates for diabetes and exophthalmic goiter for each age group (white race only) in the North and in the South. The results are presented in graphs I and II. Here is shown quite clearly that these diseases are more frequent in all age groups in the North than in the South.

The outstanding points brought out so far are that these three metabolic diseases show the same geographic differences in incidence, that for

each the area of highest death rate is found in the Great Lakes region. The total death rate from all causes is low in this area and the death rate from the various acute infectious diseases no higher than elsewhere. The diet and modes of life have no peculiar characteristics, nor is the industrial life any more intensely developed here than along the Atlantic Coast. We must, therefore, look for the cause of these metabolic disturbances in

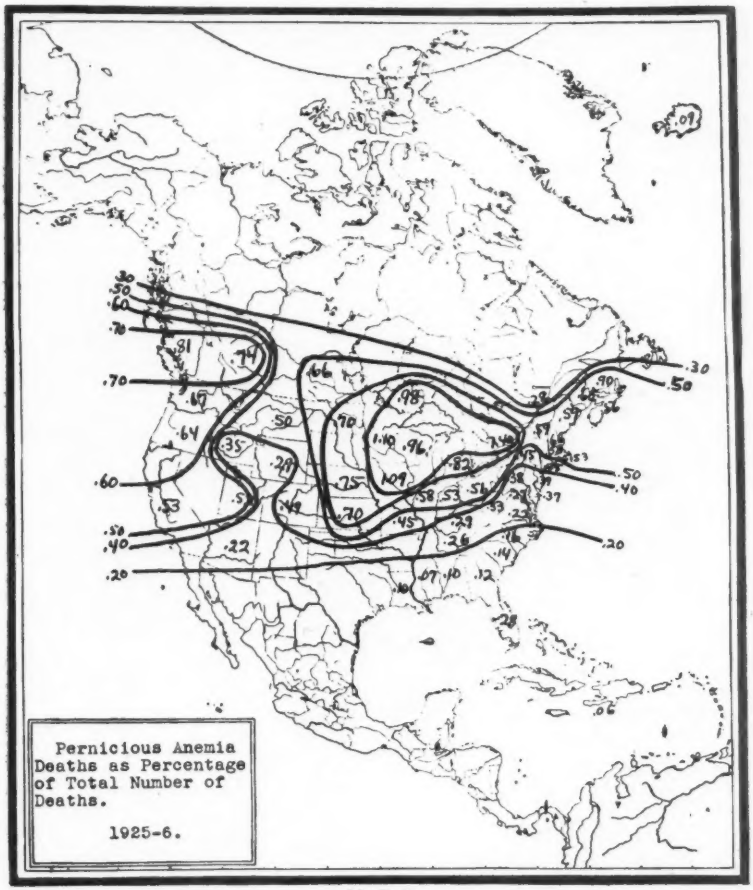


MAP I

factors outside of the population itself. And among the outside factors one would first consider the weather.

We are dealing here with diseases that may well be called over-stimulative or exhaustive diseases of metabolism. Exophthalmic goiter appears as a disease of over-stimulation of the thyroid. Several years ago (1) I showed that a cold environment in any season would cause rabbit thyroids

to assume the microscopic picture of hyperactivity, while continuous warmth brought about a change to the resting colloid type of gland. Pernicious anemia represents stimulation of the blood forming organs to the point of exhaustion, while diabetes results from failure of the pancreas to meet the level of carbohydrate metabolism demanded by the individual's activity. Probably the most stimulating element of the weather for our

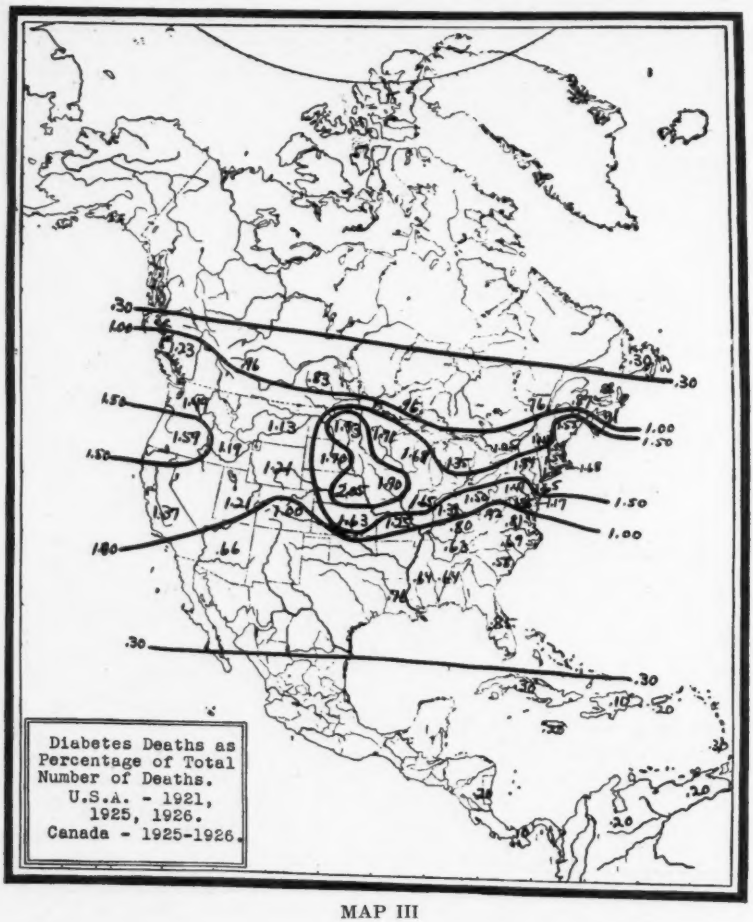


MAP II

body activity is the temperature variability. The more frequent and severe the temperature changes, the more active will the body metabolism be to meet the varying environment. One evidence of this is seen in the seasonal changes in the diabetes death rate (Graph III) and in the onset of goiter symptoms (Graph IV).

As all diabetes specialists are aware, the disorder is usually less severe

and less troublesome to the patient during the summer and fall months. This is reflected in the decline in death rate during this period as shown in Graph III, a fall which is greater than that seen in the total death rate from all causes. The onset of symptoms of goiter cases also shows a progressive decline in incidence from the late spring months through to November.* Whether it is the effect of the summer heat, the outdoor life,

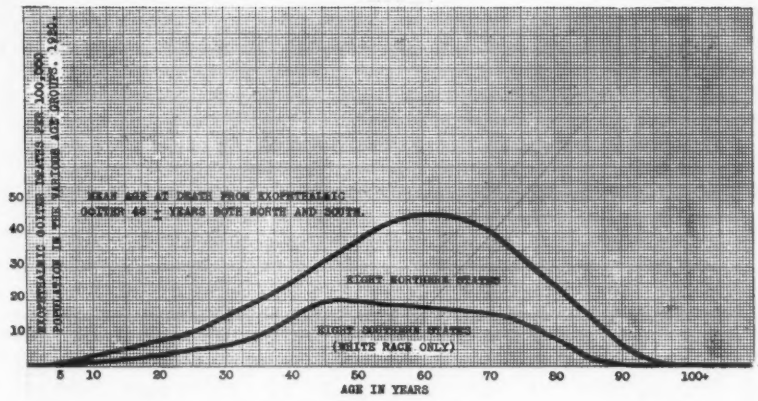


MAP III

or the less variable temperature that accounts for this lessened severity of the metabolic disease in the summer cannot be said.

Undoubtedly the most stimulating feature of the weather is the temperature fluctuation. It becomes important, therefore, to study the fre-

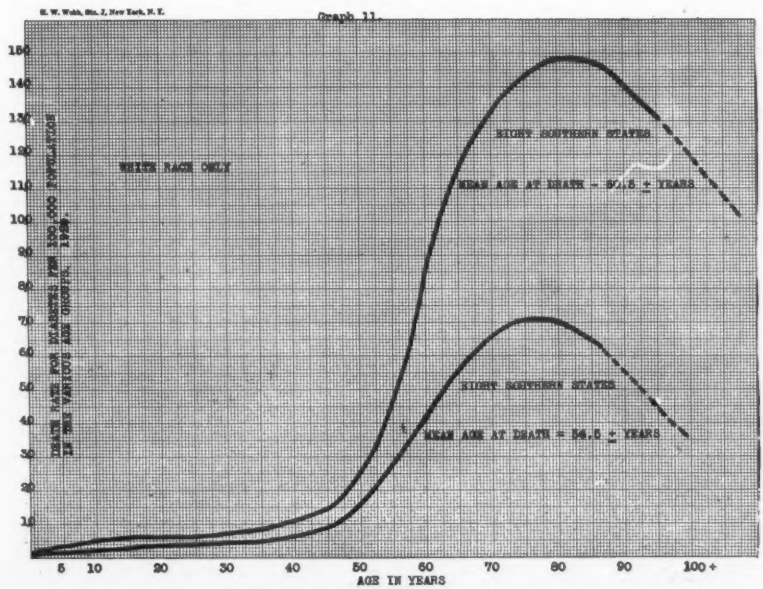
*These statistics were obtained from the Halstead Hospital records, Halstead, Kansas, through the courtesy of Doctors Hertzler and Algie. The author is much indebted to these physicians for their help in supplying this information.


MEAN AGE AT DEATH FROM EXOPHTHALMIC GOITER 40 + YEARS BOTH NORTH AND SOUTH.
EIGHT NORTHERN STATES
EIGHT SOUTHERN STATES (WHITE RACE ONLY)
AGE IN YEARS

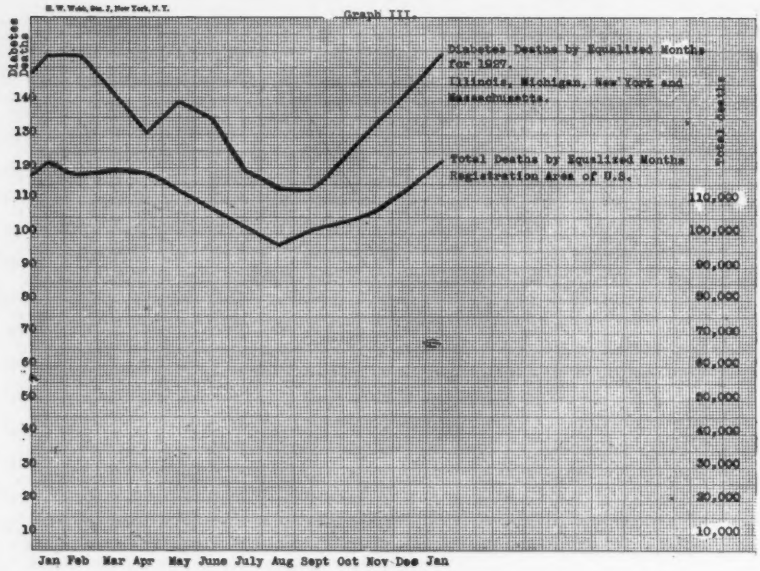
GRAPH I

quency of storms and their paths in an effort to see if they could be responsible for the observed geographic differences in the metabolic diseases.

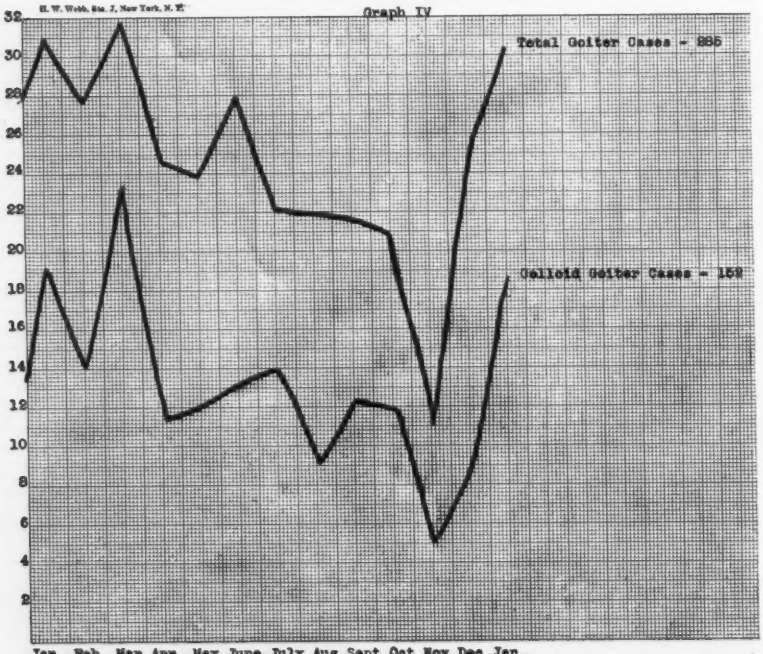
As is shown in Maps IV and V taken from Dunwoodie (2), the Great Lakes area possesses over twice the storm frequency of any other area of the earth's surface. Next comes an area including the British Isles, the Netherlands, Denmark and Northern Germany, which area possesses death rates for the metabolic diseases almost equal to those of our Great Lakes


Graph 11.
WHITE RACE ONLY
EIGHT SOUTHERN STATES
MEAN AGE AT DEATH = 57.5 + YEARS
EIGHT NORTHERN STATES
MEAN AGE AT DEATH = 54.5 + YEARS
AGE IN YEARS

GRAPH II



GRAPH III



GRAPH IV

area. In Map VI (3), the storm paths are indicated, most of them originating in the Northwest, traveling southeast, then east across the Central States to the Atlantic Coast. Thus, we see that the area of high metabolic disease incidence lies directly in the path of maximum storm frequency.

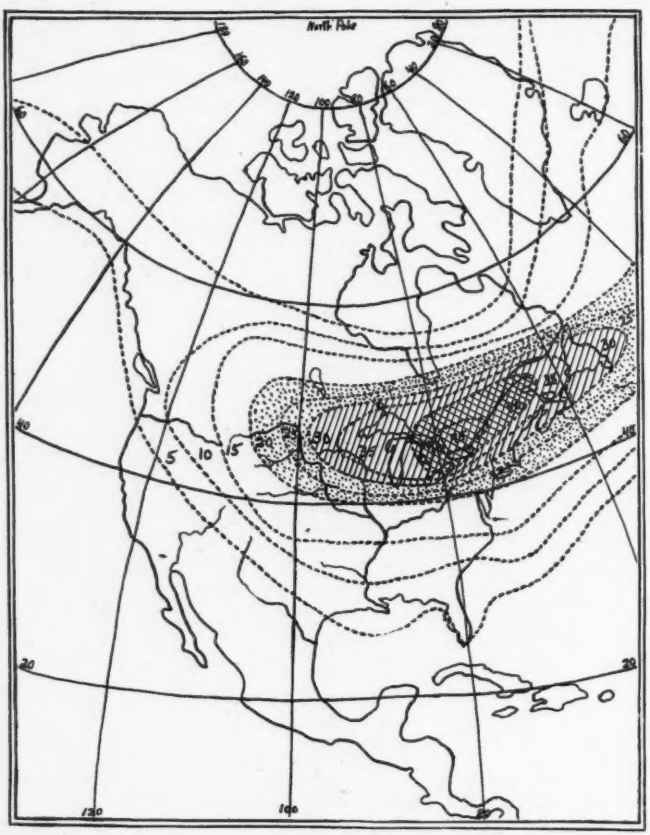
Most of the storms originating in the Northwest are accompanied by much more severe temperature fluctuations down to the Great Lakes area than along the Atlantic Coast. The severity of the temperature changes usually abates as the storms pass from the Great Lakes eastward to the Atlantic Coast. In order to get a mathematical expression of this difference I calculated the coefficient of variability of the temperature of dif-

MAP IV

ferent points over the whole continent. The details of this calculation are being published elsewhere (4) and need not be explained here. It is sufficient to say that a high coefficient indicates great variability of the temperature from day to day, while areas of only slight temperature fluctuation have low coefficients. Map VII presents these coefficients of temperature variability for different localities over North America. Such a map would be influenced both by the frequency of storms and by the severity of temperature changes accompanying each storm. According to this map the greatest stimulation should fall in the west central states and northwestward. But if we combine this map with Map V of storm frequency

we see that the maximum vigor of temperature fluctuation should fall on the Great Lakes area and slightly to the west or southwest of this area.

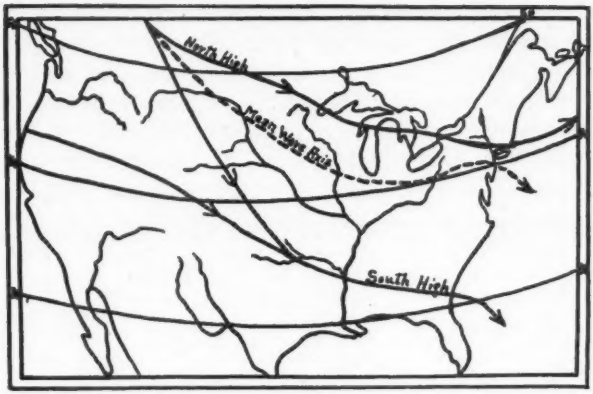
The close coincidence of this area of maximum stimulation from temperature fluctuations with the area of highest death rates from the metabolic diseases should be considered highly significant. Similar studies should be made for other continents. Present data for Europe indicate that the same relationship will hold there, although in a less striking fash-



MAP V

ion. It must be borne in mind, however, that no other known area on the earth can compare with the Great Lakes area in the vigor of its weather variability.

The second high area of metabolic stimulation is that on the Pacific Coast. I am purposely discussing this area separately from the Great Lakes area. It possesses neither high storm frequency nor high tempera-



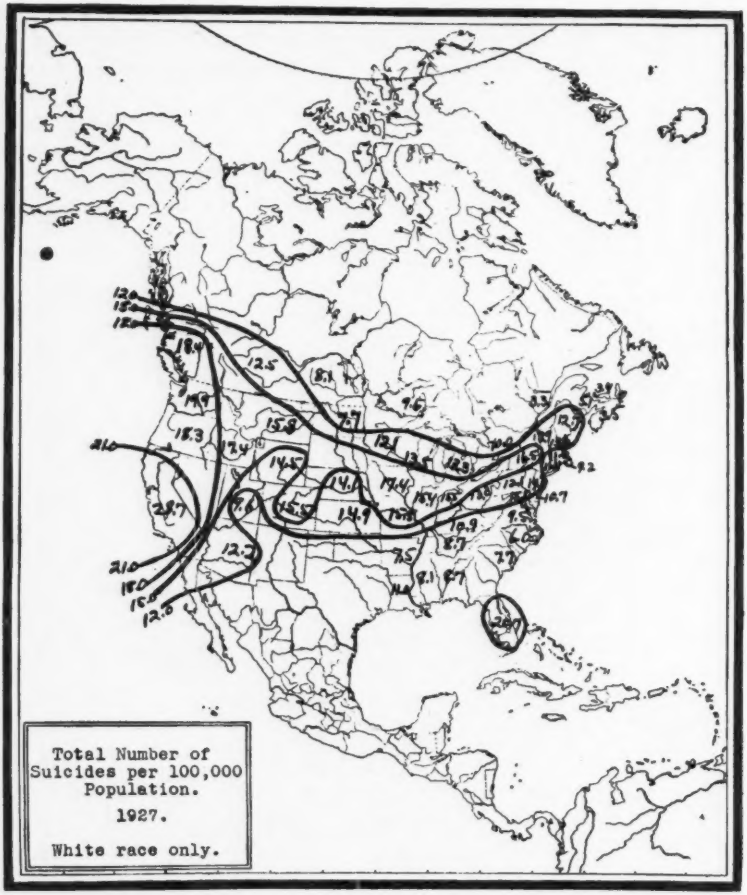
MAP VI

Map showing distribution of variability of temperature for 1925. Each value is the average of the coefficients of variability of the maximum daily temperature and the minimum daily temperature.

MAP VII

ture variability. Why, then, should it be exerting such a strong driving force on its population?

Huntington (5) in his books and articles has presented acceptable evidence that human efficiency and productivity are highest at such times and in those areas where the mean monthly temperature is near 64° F., with frequent fluctuations above and below this level. In studying the



MAP VIII

human conception rate (6) I found the same level of highest fertility at those times of year when the mean monthly temperature lay between about 50° F. and 65° F. Mean monthly temperatures above 70° F. have a definitely depressing effect on the conception rate, as do also those below 40° F.

Now the Pacific Coast from San Francisco northward is the only area in North America where the mean monthly temperature neither rises above 70° F. nor falls below about 40° F. at any time of the year. In the far north the climate is depressing by its continued low temperature, and in the south by the many months above 70° F. In the Great Lakes region both extremes are reached, with frequent wide fluctuations. In the Pacific Coast area mentioned, however, the temperature stays always near the optimum for greatest human efficiency as found by Huntington and myself. I believe that these facts account for the differences in incidence and severity of exophthalmic goiter and the other metabolic diseases in the different regions of North America. The climate in the far north and in the south is not so stimulating as to cause the body to exceed its metabolic possibilities. In the Great Lakes region however, the stimulation is too severe and we see the results in the high incidence of the metabolic diseases. In the Pacific Coast area the climatic drive is less strenuous but is applied throughout the entire year, with no depressive periods to counterbalance.

These climatic considerations hold equally well if one considers an index of mental exhaustion such as the suicide rate. Map VIII shows the same distribution of suicide frequency as was found for the metabolic diseases.

In view of all these facts I feel justified in the conclusion that climate (the temperature element in particular) is an important etiological factor in determining the susceptibility of the human race to exophthalmic goiter and the other metabolic diseases. Acute or focal infections, mental shock, emotional disturbances, etc., may play a secondary role in the actual initiation of the disturbance in individual patients. It is climate, however, which determines the susceptibility of the population in any area to these direct exciting factors. A certain number of the population are forced by the climatic drive too near the limit of their metabolic possibilities, so that it takes less of an immediately exciting force to bring on the stage of thyroid activity known as exophthalmic goiter, or the metabolic exhaustion characteristic of diabetes and pernicious anemia.

If this view of climatic effects be correct, then the metabolic disease patients should do well if sent south to endure such a climate as Miami or Havana offers. Only time and experience can say whether such will be the case.

SUMMARY

Maps of North America are presented showing the relative distribution of deaths from exophthalmic goiter, diabetes and pernicious anemia in relation to the total number of deaths. The climate of the continent is also considered with special reference to storm areas and frequencies and to the day-to-day variability of the temperature. From such maps it is observed that these three diseases are most severe in two areas, one center-

ing around the Great Lakes region, and the other covering the Pacific Northwest from San Francisco northward. The death rates in these regions are very much higher for these diseases than one sees either in the southern states or in the far north. Climate maps show the Great Lakes area to possess the highest storm frequency to be seen anywhere in the northern hemisphere, and to have great temperature variability as compared to the south. The Pacific coast, from San Francisco northward, shows a low variability of temperature and few storms, but remains at all times of the year within the limits of the optimum for human activity.

This finding of greatest metabolic break-down in the two areas where the climatic drive is exerting the greatest stimulation on humanity leads to the assumption of a causal relationship. Although infections may frequently act as the immediately exciting force to initiate these diseases, it would seem that climatic stimulation is the basic factor which determines the susceptibility of the population. Excessive stimulation brings a small number of the people too near the limits of their metabolic capacity so that they are more sensitive to the results of infection.

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THE SITE OF ACTION OF IODINE IN GOITER

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The site of action, on which the efficaciousness of iodine in the treatment and prevention of certain types of goiter depends, does not seem to have been determined. The types of goiter particularly indicated are exophthalmic and colloid, yet it is equally as valuable in most instances of adenomata with hyperthyroidism. Failures occur in all types on some occasions.

The accepted opinion seems to be that a colloid goiter develops because the amount of iodine supplied in the diet is inadequate. The gland enlarges to compensate for this deficiency by depositing colloid in the lumen of the acini of which the gland is composed. The cells regress in their activity, so that the general metabolism readings vary, if sufficient inhibition be present, toward the low normal figures. Some investigators state that the deficiency of iodine is relative to other factors.

In exophthalmic goiter there is conceded by all investigators to be an increase in the size and number of thyroid cells, as well as an increase in the number of acini. The general metabolism readings, during periods of activity, are above the normal figures.

In adenomata of the thyroid there is an increase in the number of cells in localized areas. If the cells are functioning in parallel with those of the thyroid tissue, the general metabolism readings are above the normal figure.

Iodine, if it has any direct action, in colloid goiter in view of the conception of the mechanism at play in the thyroid gland, must stimulate the cells. In exophthalmic goiter the administration leads to a decrease in the general metabolism. In this instance, if iodine has a direct action on the thyroid cells, it must act by causing a depression of the activity of the cells. The action of iodine in adenomata with hyperthyroidism, if direct, is the same as in exophthalmic goiter. In one iodine stimulates, in the other depresses. This is not the usual action of drugs, or chemicals, if given in comparable amounts.

I have been unable to find a report of the thyroid gland of a normal person who had taken iodine in large doses for some time prior to death. By a normal person is indicated an individual whose thyroid gland had never been under suspicion for goiter, and who had none of the accepted criteria of over- or under-function of the thyroid gland at the time the iodine was first administered. Iodine was administered to the patient herein discussed as a pure experiment to see if it would primarily produce any microscopic change in the thyroid cells, and secondarily to see if it

would cause any change in the size of a spleen enlarged by reason of unknown etiology.

Case 1. Mrs. L. B., a widow, aged 75, whose husband died of an unknown cause, had three children living, two of whom had a fungus condition of the skin, came under observation May 13, 1930, because of a rash on the arms and back of the neck. She had had an appendectomy when 60 years of age for pain in the right side of the abdomen. The pain had been present for 36 years, and was unrelieved by the operation. The rash had been present for about two weeks, itching and burning severely. There had not previously been a similar situation. During the preceding year the patient had been feeling weak, had become pale in color, and lost about 15 pounds in weight. The appetite was good, but she experienced soreness in the epigastrium after eating. She had a large amount of gas in the stomach and intestine, and this had increased during the six weeks preceding the examination. She had had pain in the right lower abdominal quadrant, and at times in a like position on the left side. She had had a slight morning cough for years, but this had not increased in the last few months. She was short of breath on walking. She had pain in the back of the neck at times, associated with black specks before the eyes. During the last few weeks before the examination she had been willing to sit about and do nothing, although previously she had been very active. The patient stated that for several months she had noticed a hard swelling in the left side of the abdomen. The physical examination showed the type of rash on the skin of the forearms that is typical of fungus involvement. The back of the neck showed the same type of lesions. The blood pressure was 110, systolic, and 70, diastolic. There were no signs of disease in the lungs. On the left side of the abdomen there was a large tumor extending beyond the midline and to the pelvic brim. There was a definite notch on the right margin. The surface was smooth, and the mass was generally tender. It was considered an enlarged spleen. The blood count showed a hemoglobin of 52 per cent, red cell count of 2,500,000, white cell count of 4,050, with 52 per cent polymorphonuclears, lymphocytes 47 per cent, and eosinophile, 1 per cent. The urinalysis showed albumen graded as 1, two red blood cell casts in each microscopic field, red blood cells graded as 2 and pus graded as 1. The blood serum Wassermann reaction was negative. The temperature was 98.5° F., and the pulses 72 each minute.

The culture of the saliva for fungi showed 25 inoculations positive. The colonies were white in color, and grew very rapidly. The organisms were classified as monilia. Similar types of organisms have been found in all patients with goiter that have been studied (1).

The patient was referred to various doctors in order to determine the nature of the splenic enlargement, but no explanations worthy of consideration were forthcoming. Some patients with exophthalmic goiter have a splenic enlargement. Some types of splenic enlargement are considered to be of fungal origin. An opportunity presented itself to make a clinical experiment.

The patient was given Lugol's solution in five minim doses three times each day in milk. The dose was gradually increased until she was taking 60 minims with each meal. At the end of three weeks, the spleen had become reduced about two-thirds. There were no evidences of depression or excitation of thyroid function. All cutaneous evidences of fungal involvement had disappeared, and there was practically no gas formation in the gastro-intestinal tract. It was apparent that the patient was suffering from some other factor than fungal disease.

The weakness and loss of weight increased. The patient died after 39 days of hospitalization. A definite clinical diagnosis was not made. At autopsy the patient was found to have many miliary nodules in both lungs which on microscopic examination contained mycobacteria of tuberculosis. The spleen showed similar areas. The relationship of yeast-like fungi to tuberculosis has been pointed out previously (2). The thyroid gland showed a dense sclerotic stroma with small sized alveoli, in which the lining epithelium was flattened. The picture in its entirety indicated the changes incident to the kataplastic period of life. No suggestion of tuberculosis was present in the slides examined.

The status of the thyroid gland of this patient was the same as that found in a normal individual of similar age not taking iodine. The conclusion was that the iodine had had no action on the thyroid cells. The same amount of iodine by the same method has now been administered to a large number of individuals normal so far as the thyroid gland was concerned. In one instance evidences presented themselves demonstrating that the iodine was affecting the thyroid cells per se. This patient had marked vitiligo, essential hypertension, aortitis, and was undergoing the menopause as a result of a hysterectomy for fibroids.

She developed myxedema after taking 15 drops of Lugol's solution each day for 42 days. The signs of myxedema disappeared in 23 days after the medication was discontinued. During the ensuing two years no signs of myxedema reappeared.

If a chemical has no action on a normal thyroid cell, it is presumptuous to think that in one instance it would stimulate a cell that was functioning slightly less than the normal, and in another instance depress the activity of a cell that was functioning more than the normal. The thyroid cells seem to demonstrate the "all-or-none law" in the presence of iodine. It is safe to conclude when the chemical integrity of thyroid cells is intact that the action of iodine in goiter so far as the thyroid cells themselves are concerned is extra-thyroideal.

The results obtained in goiter are due to the iodine decreasing the functional activity of the organism or organisms which led to the presence of the enlargement. McCarrison has presented evidence to justify this conclusion. Iodine is absorbed in the upper intestinal tract, so that the organism should be looked for in that region, although the same organism may be found in the colon. Yeasts are more sensitive to iodine than are bacteria. The usual amount given to goiter patients would have no action on bacteria. Iodine is important in dealing with fungi relative to their number and functional activity. The thyroid enlargement is a local expression of a constitutional condition. In exophthalmic goiter the increased number of functioning cells leads to the physical and chemical manifestations incidental to the introduction in the blood stream of an excess amount of the secretion of the thyroid cells. The same applies in adenomata that function. The phenomena are effects, not causes.

The unrelatedness of orally administered iodine to the action of the secretion of the thyroid cells has been demonstrated by the simultaneous administration of thyroid extract and iodine. The iodine did not prevent the development of the physical and chemical changes indicative of too much thyroid secretion in the body, nor did it alter these manifestations.

In animals much work has been done. There are two fields of thought. One is crystallized by the work of Chouke (3), who finds that the intraperitoneal administration of potassium iodide causes no appreciable change in the proliferative activity in the thyroid gland, neither does it produce any noticeable change in the structure or character of the colloid of the organ. The other field of thought is crystallized in the work of Mosser (4), who states that iodine increases the amount of colloid in the thyroid gland of the dog, which may eventually lead to exhaustion of the thyroid cells. Both authors quote others who have made observations similar to their own. It is, perhaps, more difficult in animals than in man to determine the presence of goiter, and the animals may have slight disturbance previous to the administration of the iodine, thereby leading to the present confusion of results.

The fact that the active secretion of the thyroid gland contains iodine lends credence to the thought that the iodine must be related directly to

the thyroid cells for is action in the various types of goiter. That this may be a fallacy is made reasonable by the use of sodium flouride, which has been found by different workers to produce the same effect as iodine on the increased metabolism of exophthalmic goiter (5). The fact that the drug has a better action when administered orally is not without significance. Among the substances that inhibit metabolic activities of yeasts sodium and ammonium flouride are mentioned by Harden (6). In my early efforts to inhibit gas formation in the stomach, which I considered produced by yeast-like organisms, I tried sodium flouride, but patients found it rather unpleasant to take. Iodine is more efficacious and much more pleasant to take. If the action of sodium flouride is found to be of value in the treatment of exophthalmic goiter by more investigators, further criteria will be at hand to establish the cause of the enlargement of the gland. The etiology of a large group of clinical conditions will thereby be made easier to understand, as all of the expressions of the same cause do not appear simultaneously, but as a train of phenomena. The study and management of phenomena, apparently independent, furnish data for interrelating the incidents, as shown by Pemberton (7) in his post-operative histories of patients with exophthalmic goiter.

SUMMARY

1. Colloid goiter is due to underfunction of thyroid cells. Exophthalmic goiter and functioning adenoma introduce an excess of thyroid secretion into the blood stream. If iodine acts directly on these cells, it would have to stimulate the former, and depress the latter two.

2. A case with autopsy is presented to show that iodine when given in large doses over a considerable period has no action on normal thyroid cells. The conclusion is warranted that iodine in goiter does not act on the thyroid cells per se, but on the cause, which is found in the upper gastrointestinal tract.

3. Iodine is shown to cause a reduction in the size of a spleen enlarged by unknown etiology.

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PATHOLOGICAL REPORT OF A CASE OF ADDISON'S DISEASE TREATED WITH CORTIN

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This is a description of the post-mortem findings in the case of Addison's disease reported by Hartman and Aaron (1).

GROSS FINDINGS

The autopsy was performed two hours after death. The skin was in general almost entirely white, due to a marked anemia. However, on the upper extremities it showed several small brownish freckles, and in some places, especially on the abdomen, around the knees, and on the thighs, it showed also a very slight diffuse brownish tint. The lips were noticeably anemic, but the gingiva of the upper and lower jaws presented very distinct patchy brownish pigmentation. The amount of fat in the panniculus was remarkably decreased. The muscles were extremely atrophic, and the long bones rather thin.

The brain, except for a slight hyperemia, was not remarkable. The pituitary, which was normal in shape, weighed 0.5 grams. With the exception of the thyroid and its contiguous structures the organs of the mouth and neck were not dissected. The thyroid was normal in position and shape, but atrophic, weighing 13 grams, rather firm in consistency and somewhat lacking in colloid. The color was dark red, and the lobular markings were well preserved. All four parathyroid glands were present and normal in shape and position. The thymus was entirely replaced by fat tissue.

The heart was slightly atrophic, weighed 185 grams, and measured: left ventricle, 1 cm. thick; right ventricle, 0.2 to 0.3 cm. thick. Along its line of closure, the anterior leaflet of the mitral valve was slightly thickened. A few chordae tendinae of the same leaflet were also thickened. Otherwise, the valves were not remarkable. The coronary arteries were patent and smooth. The endocardium of the left ventricle showed slight fibrosis.

The lungs lay free in the pleural cavity, but the medial surface of the right middle lobe was adherent to the pericardium. The visceral pleura of the left side showed distinct fresh suffusions. The lower lobe of the right lung showed typical early red and grayish-red pea-sized pneumonic foci, especially near the hilus, but also in the base. Smears showed many Gram positive streptococci. The left lower lobe in its posterior portion and near the hilus was involved in an acute active congestion. In the remaining structure of the lungs, and especially in both upper lobes and middle lobe, existed a compensatory emphysema.

The tracheobronchial lymphnodes were in general only small bean size, and almost entirely anthracotic. Examination of both lungs, tracheobronchial and broncho-pulmonary nodes did not show any signs of old tuberculosis. On cross-section of a few anterior mediastinal lymphnodes, pinhead areas, resembling fresh tubercles, were found. The same white areas simulating tubercles were also observed in the periportal, peripancreatic, mesenteric, and periaortic lymphnodes. In addition the periportal and peripancreatic nodes were distinctly enlarged, large bean size, grayish-yellow, and slightly hyperemic, especially in the medulla. A moderate number of nodes in the root of the mesentery were calcified. No caseation was present. The spleen was slightly enlarged; it weighed 230 grams and measured 35x9x6.5 cm. The markings were normal, but the consistency was slightly increased. In the surface beneath the capsule was a large pea-sized, well-encapsulated cyst filled with grayish-white detritus (old parasite?) and on the lower margin were a few deep indentations.

The pancreas was slightly atrophic and weighed 52 grams.

The stomach, except for beginning malacia, in the fundus, and a few scattered fresh pinpoint hemorrhages, was not remarkable. The gall bladder was normal; the bile ducts were patent; no stones present. The liver, which was

normal in shape, size, consistency and markings, weighed 1570 grams. Distinct capillary ectasia was present in the lower surface of the left lobe. There was still a slight amount of fat in the mesentery. The cecum and appendix showed distinct pseudomelanosis, also a few fresh hemorrhages. The Peyer's patches were distinctly visible. The small intestines showed here and there on its mucosa a few recent small hemorrhages.

The adrenals were still preserved in their shape, but markedly atrophic. Because of their thinness (1-3 mm. thick), and the excessive fat adherent to their capsule, they were barely visible. The left measured 4.5x1.5 cm., the right 4.5x1.4 cm. On cross section, no normal markings could be seen. The remaining parenchyma was grayish-red, and might possibly be related rather to medulla than to cortex. No lipoid was present. Both adrenals together weighed 3.44 grams.

The kidneys, which were normal in shape and size, showed a slight hyperemia and distinct embryonal lobulation. The bladder, prostate, testicles and rectum were not remarkable.

The aorta was normal; the width above the valves was 7 cm.; isthmus, 5.5 cm., above the renal arteries 4 cm.

The diagnosis was:

1. Addison's disease, with marked primary, genuine contraction (atrophy), or selective destruction of the cortex of both adrenals;
2. Brown pigmentary changes in the skin and mucous membrane of the mouth;
3. Distinct, apparently inflammatory, hyperplasia of the periaortic, periportal, peripancreatic, and a few mesenteric and anterior mediastinal lymphnodes;
4. Old calcification (following tuberculosis?) of several mesenteric nodes;
5. Atrophy of the thyroid and pancreas;
6. Slight atrophy of the heart;
7. Slight splenic tumor;
8. Fresh lobular pneumonia of the right lower lobe;
9. Acute congestion of the left lower lobe;
10. Recent hemorrhages in the visceral pleura (left) and in the mucosa of the stomach and intestines;
11. Pseudomelanosis of the cecum and appendix.

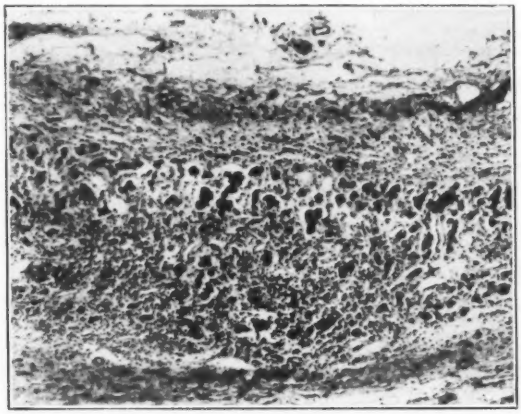
HISTOLOGY

Adrenals: Both adrenals were fixed in Mueller's solution. Frozen and paraffin sections were made and studied with fat stain, and the usual hematoxylin and eosin, Van Gieson's stain and Turnbull's Blue stain for hemosiderin. The chromaffin substance was studied in unstained frozen sections.

The most striking finding in the adrenal was practically an entire loss of cortical substance. In some sections instead of the cortex was noted a very small layer of ectatic capillaries, between which were scattered a few lymphocytes. In each of two sections we found one very small nodular formation, 1-1.5 mm. in diameter, composed of huge cortex cells containing lipoid and a few small yellow pigment granules apparently lipo-fuscin.

Some of these cells showed degenerative changes in their cytoplasm. These so-called adenomatous regenerates lay within the usual boundaries of the cortex. Other sections showed a slightly thickened capsule, but no cortical substance at all. Replacing the normal cortex was a thin, loose layer of hyaline fibrous tissue.

The width of the medullary substance was variable, ranging from a normal extent to apparently some diminution. A few sections did not reveal any medullary substance. Here the collapsed remnants of cortex were in close apposition. But we know that often in transecting different levels of normal adrenal we are confronted with similar pictures of entire lack of medulla. Kovács (2) especially stressed this point. Our impression, however, is that in general a large amount of the medulla was preserved. Recent hemorrhage, infiltrates of round cells, with a few hemo-



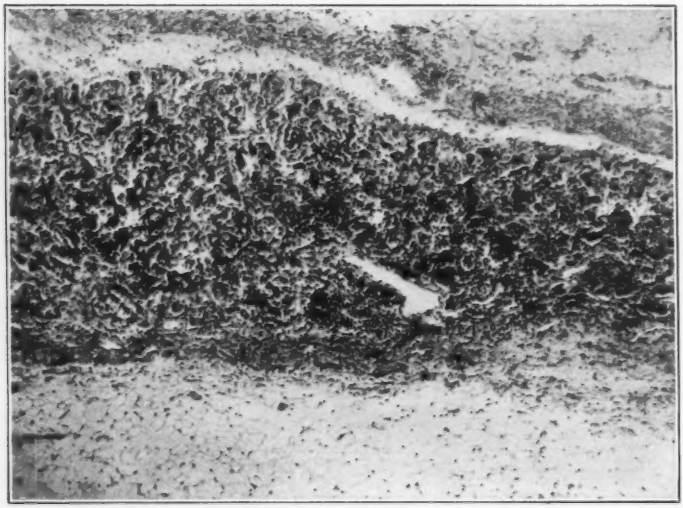
No. 1.—Cross section through adrenal—entirely preserved medulla with thin collapsed remnant of cortex and adherent fat. (Mag. low power.)

siderin cells, and a marked infiltration of lymphocytes, were noted in these preserved parts. Most of the medullary cells themselves showed a distinct chrome reaction. In certain small areas a rather young connective tissue, with a moderate number of eosinophile cells and plasma cells intervened between the thin bands of the collapsed and slightly fibrosed cortex.

The whole histological picture of the adrenals was that of a complete loss of cortical tissue, with the exception of two very small nodular regenerates which in themselves already showed degenerative changes. The cortex on both sides was replaced by thin bands of hyaline connective tissue. A striking tendency was the distinct ectasia of capillaries following the disintegration of parenchyma with subsequent capillary hemorrhage. How far the medullary substance was diminished, if at all, could hardly be determined with accuracy. Undoubtedly, a considerable number of chromaffin cells were still present. In many sections the width of

the medulla appeared normal. The infiltration of lymphoid cells, eosinophiles, and hemosiderin cells was rather marked in the preserved medulla, as well as in the area between the medulla and the collapsed and slightly fibrosed cortex. The picture corresponded to the primary or genuine contraction of the adrenal cortex, with practically the entire disappearance and attempts at regeneration of the cortical tissue, with relatively slight loss, if any, of medullary tissue, and with apparently secondary reactive cellular infiltration of the remaining adrenal tissue.

Thyroid: The lobular structure of the thyroid was well preserved. Some of the follicles which were in average rather small, contained colloid, while others were barren of colloid, showing in their lumens distinct epi-

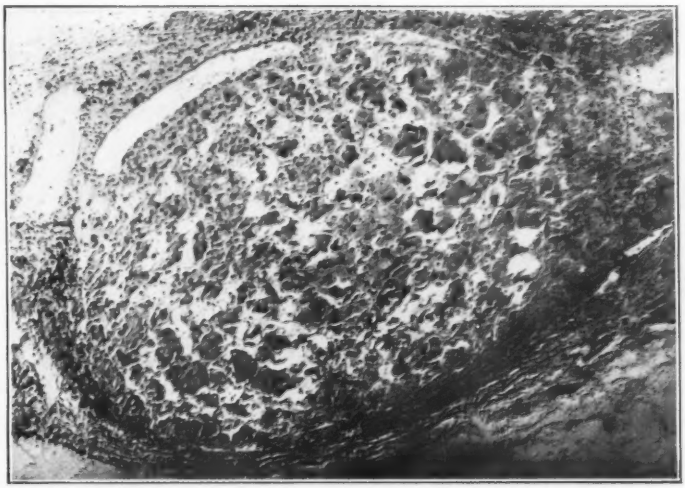


No. 2.—Cross section of adrenal—medulla of normal width, with well preserved chromaffin cells. Distinct lymphocytic infiltration. (Mag. low power.)

thelial cells, undergoing necrobiotic changes, especially in the center of the follicles. The cytoplasm of many of these desquamated cells showed fat granules. Still other follicles contained giant cells, within the desquamated follicular epithelial cells. A few large foreign body giant cells contained glistening white crystalline structures. Many of the desquamated cells had the shape of epithelioid cells. Here and there in the stroma was noted only a slight lymphocytic infiltration. No lymph follicle formations were present. The stroma was slightly increased and on section showed slight edema.

Lymphnodes: Different lymphnodes were examined, especially those hyperplastic nodes which demonstrated grossly small white areas resembling somewhat a recent tuberculous hyperplasia. In general, the structure of the lymphnodes was preserved. There were by no means signs of

a diffuse lymphoid hyperplasia. The lymphnodes showed hyperemia of the medullary substance. In some instances hemorrhage had occurred into the sinuses; the sinuses also contained rather many leucocytes. Several lymphnodes showed a few follicles with rather huge germinal centers. The aforementioned grayish-white areas were composed of growing reticulum cells, rather numerous polymorphonuclear leucocytes and apparently an increased amount of lymph fluid, containing many thread-like structures, simulating fibrin, probably caused artificially by shrinking of the protein-rich fluid. Phagocytosis of leucocytes and erythrocytes by large reticulum and endothelial cells was noted. All lymphnodes showed distinct collections of hemosiderin cells in different areas of the medulla, as



No. 3.—Small adenomatous regenerate of lipoid containing cortex cells, with scattered degenerative changes in the cytoplasm. (Mag. medium power.)

well as in the reticulum of small lymph nodules of the cortex. Finally, there was a moderate number of eosinophile cells, especially in the marginal parts of the lymph follicles. The findings were those of a distinct non-specific, inflammatory hyperplasia with signs of previous hemorrhage, and with scattered recent hemorrhage, especially in the medulla.

Kidneys: The kidneys showed around some of the glomeruli distinct lymphocytic infiltration in the interstitial tissue. No hyalinized glomeruli were found in or near these infiltrates. The capillaries between these infiltrates, both in the cortex and medulla, were filled with blood. The blood content in the capillaries of the glomeruli was normal. The epithelium of the convoluted tubules and also in some of Henle's loops, was involved in distinct degenerative changes, some tubules showing almost an entire disintegration of the epithelium, others showing distinct fatty de-

generation. A moderate number of desquamated epithelial cells and polymorphonuclear leucocytes and rarely a small albuminous cast, including a few leucocytes, filled the lumens of several tubules. No changes were noted in the small arteries and arterioles.

Testicles: Distinct signs of spermatogenesis were present.

Liver: The liver showed slight focal infiltration of lymphocytes, a few eosinophiles, and a very few leucocytes in the interlobular tissue.

Pancreas: The islands were present in the usual number without any pathological changes.

Pituitary: The normal structure was preserved. The capillaries were distinctly injected and somewhat dilated. While the eosinophiles (which were slightly atrophic) and the main cells were apparently normal in distribution and number, the basophile cells were decreased in number. Several of them showed degenerative changes. Larger than normal, these cells were coarsely granular. Their nuclei were rather small, eccentric, pyknotic, and a few contained large nucleoli. Several basophiles did not show distinct cellular outlines. The cytoplasm in some areas was involved in a large colloid droplet change to an extent apparently more frequent than normal. Scattered eosinophiles and main cells showed irregular large nuclei.

Spleen: The structure was in general normal, the Malpighian bodies being by no means increased in size.

Lungs: The lungs showed a purulent bronchitis and typical pneumonic changes, with very many polymorphonuclear leucocytes in the alveoli.

COMMENT

The histological picture of the adrenals corresponds to the so-called primary contraction of the adrenal (atrophy) as presented by Guttman (3) in his general review of the literature on Addison's disease, which revealed no other one unanimous term for this well characterized anatomical and histological lesion. Any term chosen to designate this condition adequately must convey, we feel, an idea not only of its primary pathologic anatomy, but also of its pathogenesis, without being too restricted, specific, and anticipatory, by implying data not yet definitely proven. Kovacs used the term cytotoxic suprarenal contraction. The use of the word cytotoxic, as Guttman points out, assumes too much by inferring the specific lesion is caused by a toxin hematogenously, an assumption which, though probably theoretically justified, is unproved. If by "contraction" may be understood severe "atrophy" of an organ, not necessarily with a granular surface, one would find no objection to its use for the disease in question, because the gross as well as the histological picture of the suprarenal shows generally a smooth rather than a granular surface. Yet, a few cases with nodular surfaces and fibrosis have been reported, for which the term

contraction or better, cirrhosis, would be suitable. We feel, however, that we have not yet a suitable anatomical term that appropriately describes a lesion which is now designated by so many more or less different terms. That marked progress towards finding an accurate, generally descriptive term for the pathogenetic and anatomical process is being made, can be recognized in recent attempts to express in the name the idea of a selective destruction and disappearance of the cortex. We would prefer then for the present Guttman's designation or, better still, that used by Wells (4), namely, Addison's disease with selective destruction, that is, with disintegration and disappearance, of the adrenal cortex.

An attack of scarlet fever in the winter of 1928, two years following which the patient began to show symptoms of cortical insufficiency, is the only item in the past history which can be considered of etiological significance.

Special mention must be made in this case in regard to the histological picture of the thyroid, lymphnodes, pituitary and kidneys. This case can not be employed to substantiate the statement of Wells and other writers that this type of adrenal cortex atrophy is combined with marked formation of lymphatic tissue in the thyroid. We found very marked atrophy and slight fibrosis, and some degenerative changes in the follicular epithelium, changes which can also be found in senile atrophy of the thyroid; but no lymph follicle formation.

Hyperplasia of lymphnodes and lymph follicles, especially in the intestinal tract, has been noted very often in Addison's disease. In this case there is also a distinct enlargement of several internal lymphnodes but the macroscopic picture corresponds, not to that of the so-called hyperplasia observed in lymphatic children, but more to an inflammatory hyperplasia resembling grossly somewhat early stages of a tuberculous hyperplasia. Histologically the case shows a real lymphadenitis with marked proliferation of sinus endothelial cells and with exudation of leucocytes, along with distinct signs of previous and more recent small hemorrhages into the sinuses. These lymphnode changes, to our minds, do not depend for their etiology on the acute pneumonia. Scarlet fever, with which the patient was afflicted two years previously, is very often combined with an acute generalized lymphadenophathy; perhaps some observed hemosiderotic changes could be related to a previous infective lymphadenitis. But we feel that the present picture must be explained by other factors. Whether injected cortin through its absorption is capable of producing the described inflammatory changes in the lymphnodes, or whether the changes go with the "toxic state" connected with the adrenal disease, it is too early to state. We do want to stress, however, that the lymphnode changes in this case are distinctly different from the so-called lymphatic hyperplasia.

Whether the degenerative changes in the parenchyma of the kidneys, especially in the convoluted tubules, are dependent on the recent acute

pneumonia or also on the "toxic state" cannot be determined at present. The inflammatory reaction was apparently very slight and of distinctly focal distribution.

Finally, the pituitary showed some distinct pathologic changes in addition to a slight atrophy of the eosinophile cells. These are distinct degenerative changes in the basophiles. As far as we have been able to determine from the literature, mention of similar findings has been made only by Kraus (5) in the German literature in three cases of Addison's disease.

SUMMARY

The pathological findings in a case of cortin-treated Addison's disease with selective destruction of the adrenal cortex are described. The adrenal cortex had disappeared except for two small adenomatous regenerates of lipoid-containing cortical cells. The medulla was well preserved. The thyroid showed atrophy and slight fibrosis; no formation of lymph follicles was noted. Distinct degenerative changes were observed in the basophile cells of the pituitary body and in the convoluted tubules of the kidneys. The lymphnodes were grossly hyperplastic, demonstrating histologically real non-specific inflammatory changes with signs of hemorrhage. The factors possibly concerned in the production of these latter changes, including the rôle of injected cortin, are considered.

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Abstract Department

Glutathione in the adrenal during gestation (Le glutathion du tissue surrénal au cours de la gravidité). Blanchetiere, A., L. Binet and A. Arnaudet, Compt. rend. Soc. de biol. **104:** 163. 1930.

In dogs, the glutathione content of adrenal tissue increased as pregnancy advanced.—J. C. D.

Observations on the cortico-adrenal hormone. Britton, S. W. and H. Silvette, Am. J. Physiol. **97:** 507. 1931.

Extracts of the adrenal cortex have been made according to the method of Swingle and Pfiffner, and their effects noted on cats, dogs, rabbits and rats. In a few cases tests on man have also been made. The extracts have been proved to contain significant amounts of the cortico-adrenal hormone. The survival period of adrenalectomized cats is at least much prolonged, and may possibly be extended indefinitely, by daily injections of the extract. Treated animals gain in weight and appear normal. The extracts usually contain only one in two million parts of adrenalin, and the results are not produced by the adreno-medullary hormone. Particular attention has been given to recovery from the severe terminal symptoms of adrenal insufficiency. Evidences of resuscitation of adrenalectomized cats from extreme prostration following intraperitoneal injection of the Swingle-Pfiffner extract are apparent in 15 to 30 minutes: convulsions are abolished, the animals show an interest in their surroundings and attempt to sit up; within an hour or so they may walk about and appear practically normal, and two hours after injection they may take food. Probably of considerable importance are the increases in blood sugar to normal levels which are found to take place during the course of recovery. Usually it has been necessary to inject from 5 to 10 cc. of extract (1 cc.=40 grams fresh whole gland) per kgm. body weight of the animal, in the course of 24 hours, to effect restoration from the pronounced symptoms of adrenal insufficiency. These doses represent relatively huge amounts of cortical tissue—two thousand times or more than the amount present in the normal cat. Twenty cubic centimeters of the extract given intraperitoneally to a small (two kgm.) cat have produced no ill effects. The material is also non-toxic when given subcutaneously, intramuscularly, intravenously, or intracardially. We have used the extract subcutaneously and intramuscularly in man without ill effect. The method of Hartman and his co-workers has also been used by us in the preparation of several batches of cortico-adrenal extract. This material, tested a great number of times on adrenalectomized cats, has given in only a few cases an indication that it contains in small amount the hormone of the adrenal cortex. The Swingle-Pfiffner extract is effective on cats by mouth. Dogs are stimulated to carry out two to three times as much work under its influence. Its injection produces sexual precocity in rats.—Authors' Abst.

The effect of diverting adrenal vein blood into the portal vein on blood sugar. Dragstedt, L. R. and J. C. Ellis, Am. J. Physiol. **97:** 517. 1931.

An anastomosis was made between the vena cava and portal vein in 11 dogs. The vena cava was ligated central to the anastomosis. This produced a temporary diversion of adrenal vein blood into the portal vein and caused a hyperglycemia of greater extent and longer duration than control operations. An anastomosis similar to the one described above was made in four dogs and the vena cava ligated. Subsequently by means of several stage operations, both lumboadrenal veins distal to the gland were tied off and the vena cava again tied off, this time below the entrance of the renal veins. This operation produced a permanent diversion of adrenal vein and renal vein blood into the portal vein. The blood sugar remained above normal for from 30 to 90 days and the daily variations were much wider than those obtained in normal animals. Glycosuria was not produced.—Authors' Abst.

Experimental suprarenal exhaustion. Edmunds, C. W. and R. G. Smith, Proc. Am. Assoc. Physicians, Abst., J. A. M. A. **96**: 1986. 1931.

In experiments on epinephrine storage it was found that there are certain poisons which may increase epinephrine in the blood, as, for instance, pilocarpine and strychnine, but there is no diminution in the gland. Stimulation of the splanchnics can increase blood pressure, without diminution in the gland. Dogs receiving 2 mgm. of physostigmine per kilogram of body weight have serious reduction of the epinephrine and become very weak. If the poison is withdrawn, the substance in the gland is quickly replaced and is normal in forty-eight hours.

Effect of injections of cortin on resistance of suprerenalectomized rats to large amounts of histamine. Gottesman, J. M. and D. Perla, Proc. Soc. Exper. Biol. & Med. **28**: 1022. 1931.

In the following experiments an effort was made to increase further the resistance of suprarenalectomized rats to very large amounts of histamine, by injections of cortin. Suprarenalectomized adult rats were injected daily from the day of operation with 1.5 to 2 cc. daily of cortin (1 cc. was the equivalent extractive of 40 gm. of cortex). On the 6th day after operation 5 rats were injected with 600 mgm., 3 with 700 mgm. and 8 with 800 mgm. of histamine per kgm. of body weight. Three normal rats received 900 and 950 mgm. of histamine per kgm. of body weight. Of the 5 rats injected with 600 mgm. of histamine per kgm. all survived. Of the 3 rats injected with 700, 2 survived, and of the 8 receiving 800, 3 survived. The normal rats were killed with 950 mgm. per kgm. From these results it is apparent that it is possible to raise the resistance of suprarenalectomized rats in many instances almost to the normal level of resistance of normal rats by repeated injections of large amounts of cortin. The effect of cortical hormone on the resistance of suprarenalectomized rats is a specific one. Previous work has shown that large amounts of saline have no demonstrable effect on the resistance of suprarenalectomized rats. Repeated injections of epinephrin have only a very slight effect. An extract of the spleen made in the exact manner as the cortical extract failed to produce any increase in resistance of suprarenalectomized rats. The female sex hormone of Doisy (theelin, Parke, Davis & Co.) and the male sex hormone (Funk and Harrow) did not raise the resistance of suprarenalectomized rats. The action of cortin on the resistance of suprarenalectomized rats to histamine and other toxins and poisons is a measure of specific activity of the life-prolonging hormone of suprarenal cortex.—D. Perla.

Immunological studies in relation to suprarenal gland. VII. Effect of bilateral suprarenalectomy on acquired resistance in rats. Gottesman, J. M. and D. Perla, Proc. Soc. Exper. Biol. & Med. **28**: 648. 1931.

Repeated injections of typhoid vaccine prior to suprarenalectomy raise the resistance of rats to more than 10 M.L.D. for suprarenalectomized rats. Suprarenalectomy apparently does not diminish the acquired resistance to typhoid vaccine, though it markedly depresses the natural resistance. It has been shown that Bartonella muris infection in the adult splenectomized rat cannot be transmitted to the suprarenalectomized rat of infected stock. The rat is spontaneously infected with Bartonella muris anemia early in life, between the fourth and sixth week. It then becomes a carrier of the Bartonella muris and possesses an acquired immunity to the infection. The infection following splenectomy in the adult carrier rat is indicative of a depression in the acquired resistance to Bartonella muris. It has been further shown that the acquired resistance to Trypanosoma lewisi of normal rats as a result of a previous infection is uninfluenced by subsequent suprarenalectomy. These observations indicate that once a cellular or humoral immunity is established to an infection or an antigenic substance this acquired resistance cannot be broken down by subsequent suprarenalectomy. Bilateral suprarenalectomy, though markedly depressing the natural resistance of the adult albino rat to toxins, poisons and bacterial and protozoan infections, does not affect the acquired resistance resulting from previous injections of such substances Acquired and natural resistance are dependent on different physiological processes in the organism and are not merely quantitative variations of the same process as is generally assumed.—D. Perla.

The vital hormone of the adrenal cortex. Hartman, F. and Katharine A. Brownell, Am. J. Physiol. **97**: 530. 1931.

A concentrated extract containing the vital hormone of the adrenal cortex can be made by the very simple process of extraction with ethyl ether and ethyl alcohol. This extract is not toxic and contains but a small amount of epinephrin. Completely adrenalectomized cats can be kept alive in good condition by the injection of such an extract. One cat was kept alive for nearly nine months, dying because the extract was diminished. The adrenals need not be removed in two stages to insure survival. If an adequate amount of extract is given through the critical stage cats with both adrenals removed at one operation do as well as those operated upon in two stages. Adequately treated adrenalectomized animals behave in every way like normals. Young animals grow to maturity and successfully raise litters (rats). The vital hormone enables adrenalectomized rats to resist cold almost as well as normals. Normal rats, cortin-treated adrenalectomized rats, and adrenalectomized rats injected with an equal volume of salt solution were exposed to a temperature of 10° C. for ten hours. The average temperature fall was as follows: Normals, 38.6 to 36.88° C.; cortin treated, 37.76 to 35.33° C.; NaCl treated, 37.24 to 27.28° C. The cortical hormone raises the resistance of adrenalectomized rats to bacterial toxins. A majority (71%) of cortical treated rats survived the injection of a dose of typhoid vaccine which killed all of the controls. Likewise we have been able to show an increase in the resistance to chronic intoxication from bacterial toxins. Cats allowed to pass into the last stages of adrenal insufficiency which just precede death have been revived by cortical extract. A subject of Addison's disease with notably dubious prognosis was revived and has been kept alive for eight months by injection of this extract. Two cases of toxic goiter have shown improvement with similar treatment. Two cases of muscular atrophy have been benefited by cortical extract. Fibrillation of skeletal muscle has disappeared and the general condition has much improved. Cortical extract increases the threshold for fatigue in the asthenia not only of Addison's disease and toxic goiter but in some other conditions. In one patient, the amount of work (by ergograph) which could be accomplished without fatigue was ten times greater after a few days' treatment than it was before.
—Authors' Abst.

Acute suprarenal insufficiency with aspects of acute peritonitis (Akute Nebennierenninsuffizienz unter dem Bilde akuter Peritonitis). Mandl, G., Med. Klin. **27**: 50. 1931.

Report of a patient, age 85 years, who, after 4 days of anorexia, developed acute abdominal symptoms. Severe pain and vomiting suggested ileus or probable peritonitis. A hypodermic administration of 0.01 gm. morphine was followed by quiet sleep within a few minutes. One-half hour later the patient died. Autopsy revealed bilateral tuberculous caseation of the suprarenal glands. There were none of the characteristic symptoms of Addison's disease during life. The author believes that this case supports the statement of Lewis and of Scott, alleging a very marked increase in toxicity of morphine in adrenal insufficiency.—J. M. Rogoff.

Injections of cortin on resistance of suprarenalectomized rats. Biological assay of extracts of suprarenal cortex. Perla, D. and J. M. Gottesman, Proc. Soc. Exper. Biol. & Med. **28**: 475. 1931.

The resistance of suprarenalectomized rats to toxins, poisons, bacterial and protozoan infections is markedly depressed. The height of susceptibility is reached at the end of the first week following bilateral suprarenalectomy. Suprarenalectomized rats succumb to small doses of typhoid vaccine. In previous experiments typhoid vaccine has been used as a gauge of suprarenal insufficiency. The protective effect of an extract of the cortex of the suprarenal gland prepared by us according to the method of F. A. Hartman was determined. Three-months-old adult suprarenalectomized rats were used. Injections of a highly concentrated extract of cortex were administered twice daily intraperitoneally. The M.L.D. for suprarenalectomized rats of a batch of typhoid vaccine was determined. Rats that had been repeatedly injected with cortical extract survived as much as 4 M.L.D. of typhoid vaccine. Rats that had received cortical extract only during the last 24-hour period survived one M.L.D. of typhoid vaccine. Rats that had received no cortical extract or had

been injected with salt solution were killed by one M.L.D. of typhoid vaccine. Most of the rats in these 2 groups lost from 10 to 40% of their body weight during the first week after operation. All the rats that had been repeatedly injected with cortical extract equalled or surpassed their preoperative weight by the sixth day after the operation. These experiments indicate that the cortical extract of Hartman raises the resistance of suprarenalectomized rats. Though a single injection of a large amount of cortin may maintain the weight curve for a week, it will not raise the resistance as high as repeated injections of small amounts of cortin. The effect of an extract of cortex on the resistance of suprarenalectomized rats to typhoid vaccine may be used as a biological assay of the potency of such extracts. A standard rat unit may thus be readily established for each batch of cortical extract. Since those rats treated during the last 24 hours prior to the injection of typhoid vaccine show increased resistance to typhoid vaccine, a rat unit of cortical extract may be established as that quantity of extract necessary to raise the resistance of suprarenalectomized rats sufficiently to survive the M.L.D. of typhoid vaccine injected on the sixth day following the operation.—D. Perla.

Effect of injections of cortin on resistance of suprarenalectomized rats to histamine poisoning. Perla, D. and J. M. Gottesman, Proc. Soc. Exper. Biol. & Med. **28**: 650. 1931.

In the following experiments the effect of injections of cortin on the resistance of suprarenalectomized rats to histamine (ergamine acid phosphate, Burroughs Wellcome) was studied. Previous work had shown that suprarenalectomized rats are highly susceptible to histamine poisoning. It was suggested that histamine could be used as a gauge of suprarenal insufficiency. Adult suprarenalectomized rats are killed by 100-120 mgm. of histamine per kgm. when administered on the 6th day after operation. Normal rats survive 700-900 mgm. per kgm. Preliminary tests in the present studies indicated that immature suprarenalectomized rats will resist larger amounts of histamine than mature suprarenalectomized rats. The minimal lethal dose of histamine for suprarenalectomized 6-week-old rats is between 150 and 200 mgm. per kgm. of body weight. The minimal lethal dose of histamine for suprarenalectomized adult rats is between 100 and 120 mgm. per kgm. of body weight. The daily injections of cortin (0.5 cc. twice daily) raised the resistance to at least 3 minimal lethal doses of histamine. (1 cc. of cortin is equal to 40 gms. of cortex.) The administration of cortin (1 cc. twice on the 5th and 6th day) during the last 24-hour period prior to the injection of histamine will raise the resistance of suprarenalectomized rats to at least 3 minimal lethal doses of histamine. These experiments further demonstrate that repeated injections of cortin raise the natural resistance of suprarenalectomized rats to poisons as well as bacteria. It is evident that the marked susceptibility of suprarenalectomized rats to histamine poisoning is not due to epinephrine insufficiency as maintained by Wyman but to cortical insufficiency. The protective action of cortical extracts against histamine poisoning in suprarenalectomized rats is a better means of biologically assaying the potency of such extracts than typhoid vaccine suggested in a previous communication. Ergamine acid phosphate (histamine) is a standard chemical that varies very little in toxicity. The amount of cortical extract injected intraperitoneally into suprarenalectomized albino rats on the 5th and 6th day after operation necessary to protect these rats against 200 mgm. of ergamine acid phosphate (Burroughs Wellcome) may be considered as a standard unit.—D. Perla.

A substance in urine of normal human adults that raises the resistance of suprarenalectomized rats. Perla, D. and J. M. Gottesman, Proc. Soc. Exper. Biol. & Med. **28**: 1024. 1931.

It occurred to the authors that the cortical hormone may be eliminated in the urine in large amounts. A lipoid extract of the urine of normal young adults, males and females, was made. The urine of young male and female adults is extracted with benzene. The benzene fractions are evaporated at 40 degrees in vacuo to dryness, the residue taken up in ether, the ether evaporated off in vacuo and the residue taken up in water or oil. It is non-irritating when injected subcutaneously or intraperitoneally and has no odor of urine. The procedure takes 36 to 48 hours. The final product was made up so that 1 cc. of the extractive was equivalent to 300 cc. of urine. The effect of repeated daily injections of the extract on the resistance of suprarenalectomized

rats to histamine poisoning was determined in the same manner and under the same conditions as extracts of the suprarenal gland in our previous experiments with cortin prepared from the cortex of the whole gland according to the method of Hartman. It was found that the resistance of suprarenalectomized rats was raised to 4 M.L.D. of histamine for suprarenalectomized rats by repeated injections of the urine extract. It is estimated that one liter of urine furnished an equivalent amount of protective substance in about ½ pound of whole gland. The extractive obtained from the urine contains a substance that has some of the physiological properties of cortex of the suprarenal gland. In previous experiments we found that an increase in resistance in suprarenalectomized rats following administration of cortin is a specific one. As with the cortical preparations, young adult suprarenalectomized rats injected with the extract from the urine gained from 8 to 10% in weight during the first week following suprarenalectomy. The suprarenalectomized untreated rats either lost weight or their weight remained stationary. Preparations made from other organs such as the spleen in the manner of cortin, and theelin, the female sex hormone of Doisy, and the male hormone of Funk and Harrow, fail to raise the resistance of suprarenalectomized rats. Experiments are in progress to determine the effect of this extract of the urine on suprarenalectomized cats.—D. Perla.

On the cortical hormone of the adrenal gland. Swingle, W. W. and J. J. Pfiffner, Proc. Soc. Exper. Biol. & Med. **28**: 511. 1931.

Extract made from whole adrenal glands is as effective in combating adrenal insufficiency and as low in adrenalin content as are preparations of cortex alone. A new method for separation of adrenalin from the cortical hormone is described. It consists in distributing an active fraction between aqueous alkali and an immiscible solvent such as benzene or ether. Adrenalin passes into solution in the aqueous alkali whereas the cortical hormone is found in the immiscible solvent phase. By means of the above fractionation step, highly active extracts (1 cc. equivalent to 30 grams of cortex) have been prepared, containing less than one part of adrenalin in 4,000,000. The cortical hormone is thermolabile and is destroyed by boiling an active extract in an open flask for two minutes. Cortical extracts prepared with permutit fractionation give a negative biuret, ninhydrin, Hopkins-Cole, Molisch, Pauly and Liebermann-Burchard reaction. They give a positive xanthoproteic, Millon's alkaline copper, and alkaline phosphotungstate reaction. These four positive reactions can be accounted for by the presence of traces of phenolic decomposition products of adrenalin. Cortical extracts, if preserved with 0.1% benzoic acid, retain their potency for long periods at room temperature. Tests of the potency of fractions containing the cortical hormone which had been stored in benzene for 12 to 15 months, show that they retained much of their activity during this period, although they are apparently somewhat less potent than freshly prepared material.—W. W. Swingle.

Vascular responses to histamine in suprarenalectomized rats. Wyman, L. C. and Caroline T. Suden, Am. J. Physiol. **97**: 571. 1931.

Intravenous injections of histamine produced depressor responses to all doses tried, the minimal effective dose being about 0.0001 mgm. Microscopic observation of intestinal blood vessels showed only dilator reactions to intravenous histamine. Increased susceptibility to histamine poisoning follows immediately the removal of the influence of the suprarenal medulla from the circulation by excision or ligation of the glands. The minimal intravenous dose of histamine necessary to produce a permanent fall of blood pressure is from 0.3 to 0.5 mgm. per 100 grams of body weight for normal or blank operated rats, and from 0.05 to 0.1 mgm. per 100 grams for suprarenalectomized rats, or rats having autoplastic cortical transplants or gross accessory cortical tissue but no demonstrable chromaffin tissue. Subcutaneous injections of adrenalin, 0.02 mgm. per 100 grams body weight, twice daily during seven days following suprarenalectomy, the last injection being given two hours prior to the injection of histamine, did not materially affect the vascular responses. The majority of these rats showed responses similar to those of untreated rats having no demonstrable chromaffin tissue. In a few cases the initial blood pressure was higher and the reactions to histamine not so marked as in the case of suprarenalectomized rats with no previous treatment. Exactly similar results were obtained, however, in a series of suprarenalectomized rats which received

a single subcutaneous injection of adrenalin two hours prior to the injection of histamine, indicating that in the first series the last injection of adrenalin may have exerted a pharmacological effect in some cases on the subsequent responses to histamine. It is believed, therefore, that the influence of the suprarenal medulla in protecting the rat from the fatal effects of histamine poisoning is effective by virtue of the antagonism between secreted adrenalin and histamine, rather than that the protective action of adrenalin is dependent on a continuous effect maintaining the nutrition or tone of some part of the vascular neuromuscular mechanism.—Authors' Abst.

Response of the reticulocytes in the treatment of two patients with pernicious anemia fed organic material obtained from the suprarenal cortex. Zerfas, L. G. and A. Koehler, Proc. of the Central Society for Clin. Research. Abst., J. Clin. Investigation, **8**: 663. 1929-30.

An organic substance obtained from the suprarenal cortex, when fed to two patients with primary anemia during relapse, in amounts of 33 mgm. 3 times daily, produced reticulocyte responses similar to those obtained with the feeding of liver, kidney, stomach or fractions of liver. Following the reticulocyte response, the red blood cells increased in number approximately equal to the number of young cells appearing in the blood on the day of the peak. There was little, if any, clinical improvement in the patients, and the continued feeding of the preparation did not produce a further increase in the total number of red blood cells. Subsequently, these patients were given adequate daily amounts of liver extract No. 343, and in each instance the clinical improvement was marked and the level of the red blood cells reached normal. This suggests the possibility that the mechanism of producing a remission of the red blood cells in primary anemia is not entirely dependent upon the initial delivery of reticulocytes into the circulation, but is probably associated with a growth-promoting substance not present in the organic material obtained from the suprarenal cortex, but present in liver, kidney, and potent fractions of liver.

Obesity. Barborka, C. J., M. Clin. North America, **14**: 701. 1930.

The problem of obesity is difficult because, as Du Bois has stated, there is no stranger prenomenon than the maintenance of a constant body weight under marked variations in bodily activity and consumption of food. Few scientific data are available to explain maintenance of normal weight. Many factors, such as disturbance of endocrine glands, water metabolism, specific dynamic action, and fluctuations in basal metabolism have been held responsible. Such data as Newburgh has recently presented in determining the total heat elimination and total water exchange, with accurate studies of the nature of obesity, do not lend support to the conception of a mysterious economy practiced by the tissues infiltrated with fat. Whatever the mechanism of obesity may be, the clinical fact remains apparent that two persons on the same intake may vary in response, one getting fat and another remaining thin. Underweight in the otherwise healthy person also occurs even when the intake of calories is more than sufficient to supply the demands for energy. The so-called "constitutionally" obese person and the healthy person who is underweight may present extremes of the same problem. The difference between the so-called "exogenous" and "endogenous" types of obesity is only one of degree, not of kind, and both are the result of disturbed metabolism which, in the last analysis, is probably due to some glandular dysfunction which alters the relation between intake of food and expenditure of energy.—I. B.

Feeding experiments on tadpoles with endocrine glands taken from young and old cattle (Untersuchungen ueber den Einfluss der Ernaehrung mit Einigen Organen mit innerer Sekretion von Jungen und alten Tieren auf die Entwicklung von Froschkaulquappen). Dessy, G., Endokrinologie, **7**: 432. 1930.

The author studied the influence of various glands of internal secretion on tadpole development (species not mentioned). The endocrine material was taken from cattle. The aim of the experiment was to search for possible differences in the activity of young (2-12 months) and old (7-9 years) organs. Thyroid, thymus, suprarenal (entire), testicle, ovary, pancreas, and heart muscle for control, were fed as dried powders. Two series, young (A) and old (B) tissues, 30 animals per series, 10 per dish were arranged. Each 10 re-

ceived daily 0.25 grams of substance. Thyroid: there was little difference between A and B. In A the hind limbs seemed to appear sooner than in B; fore-limbs sooner in B. Old thyroid appeared to be considerably more toxic than young. Thymus: in B, hind limbs appeared later than in A. Fore-limbs were only rudimentary. Thymus toxicity was very high, in disagreement with the observations of other authors. Suprarenal: toxicity of old gland was very high. Metamorphosis appeared much later in A than in B. Ovary: no difference between A and B. The substance was rather toxic. Testicle: no toxicity. Development and metamorphosis proceeded normally. Pancreas: in B the rate of development was somewhat faster. Little toxicity. Heart muscle: in B there was much faster development, almost twice as fast as in A.—F. Gudernatsch.

Endocrinopathies: Thyro-pituitary syndromes; diagnosis and treatment. Eidelsberg, J. M. Clin. North America, **14**: 425. 1930.

This is a brief discourse on the clinical application of the various interglandular relationships with special emphasis on thyro-pituitary dysfunction. Three cases are described in detail to illustrate the results of thyro-pituitary disturbances in childhood and adolescence. Pituitary gland involvement must be considered from the standpoint of whether anterior or posterior lobe disturbance predominates. In treatment it is well to guard against undertreatment by thyroid substance. Also, anterior pituitary substance must be given in large doses—15 to 45 grains daily. In extreme cases, anterior pituitary may be given by injection, 1 cc. daily, in mild cases 2 or 3 times a week. In posterior lobe deficiency cases, smaller doses are given. The best results are by a combination of oral and hypodermic treatment. Prognosis is good in those fortunate enough to be treated early. Even in those having reached adult life, much can be gained by appropriate treatment. In making our diagnosis of these syndromes, we consider the various glandular components separately. Thyroid deficiency is considered a possibility if we find the following earmarks: Coarse, scanty hair on the head, lanugo-like hair on the body, "saddle-back" type nose, large tongue, pot-belly, umbilical hernia, subnormal temperature, pale skin, constipation, and a basal metabolism rate below minus 10%. The number of these stigmata found in any one case depends on the degree of deficiency and its duration.—I. B.

The effects of deficient water-intake on the growth of the rat. Jackson, C. M. and V. D. E. Smith, Am. J. Physiol. **97**: 146. 1931.

Young rats were held at nearly constant body weight for several months by a restricted water-intake, allowing food ad libitum. These test rats showed a progressively decreasing requirement for water up to the second or third month of the experiment, after which there was a tendency toward a slightly increasing requirement. The food consumption was roughly parallel with the water-intake. These test rats became emaciated, with changes in appearance and in organ weights resembling those previously found by Kudo in similar but shorter tests. The organs also became variably dehydrated. "Restricted food" controls were given (with water ad libitum) the same amount of food as was voluntarily consumed by the corresponding test rats. These control rats made a remarkable gain in body weight, ranging from 33 to 98%. This gain was due solely to the increased water-intake, since the other factors were held constant. These "restricted food" controls also became emaciated, but the changes, including those in organ weights and dehydration, were in general somewhat less than were found in the corresponding test rats. These differences likewise must be ascribed to the increased water-intake. The importance of the water-intake in growth, independent of the food consumption, is thus demonstrated.—Authors' Summary.

Experimental and clinical studies concerning the action of hormones in gynecology (Experimentelle und klinische Studien zur Hormonwirkung in der Gynäkologie). Hauptstein, P., Munchen. med. Wchnschr. **77**: 1223. 1930.

Confirmation is given of Zondek's and Aschheim's findings concerning the stimulating influence of the mature anterior pituitary lobe upon ovulation. The infantile and fetal anterior lobes also contain the active substance, though in smaller amounts. The quantitative relationship of the amounts of active

substance in the fetal, juvenile and mature stage is approximately 1.0:2.5:10.0. It is not clear why the presence of the active substance does not exert any effect upon the sexual glands before sexual maturity. Some of the author's experiments gave evidence that the thymus gland does not inhibit the inefficiency of the anterior lobe hormone. There does not exist any proof for the assumption that the cyclic changes in the sexual organs are due to cyclic changes in the production of anterior lobe hormone. Anterior lobes of cows in all phases of the cycle were found to be active. It is not possible to produce a continuous oestrus by administration of large amounts of anterior lobe hormone no matter in which phase it is given. Implantation of corpus luteum influences the oestrus cycle of mice only when there is used a corpus luteum beyond the height of its maturity, particularly corpus luteum persistens or corpus luteum graviditatis of the first half of pregnancy; in these cases the oestrus cycle was inhibited for a time up to 38 days (instead of three to five days normally). Treatments with ovarian hormone were successful with effects lasting for one-half up to one and one-half years in various kinds of disorders. The dosage turned out to be rather unimportant. Thirty-six to eighty thousand mouse units were given with quite irregular effects. The large doses did not affect blood pressure, pulse rate and kidney function. The best time to start the treatment of hypo-hormonal disorders is about the middle of the cycle between menstruations and the best moment for stopping the treatment is shortly before the beginning of the expected menstruation.—W. Raab.

Carbohydrate metabolism in Mongolian idiots as evidence of endocrine dysfunction. O'Leary, W. D., Am. J. Dis. Child. **41**: 544. 1931.

Sugar (glucose) tolerance tests were made on 18 Mongolian idiots at the St. Louis Training School for Mental Defectives. The object of this work was to determine if pituitary hypofunction, as claimed by Timme, could be demonstrated in these individuals by the presence of the high sugar tolerance which usually accompanies underfunction of the pituitary. Fourteen of the patients received mixed gland treatment of thyroid 1/5 gr. (0.13 gm.), whole pituitary 1/5 gr. and anterior pituitary 1 gr. (0.065 gm.). Most of these had a very low sugar tolerance, a few of the curves being of the diabetic variety, while a few were practically normal. Four patients had received no glandular treatment and all these gave curves indicative of a very high tolerance. The difference between the average curves of the two groups was very striking. Three of the treated cases with the lowest tolerance were given raw liver for a week or ten days, after which time the tolerance curves were markedly altered toward a higher tolerance.—Author's Abst.

Studies on the physiology of lactation. I. The relation of lactation to the ovarian and hypophyseal hormones. Nelson, W. O. and J. J. Pfiffner, Anat. Rec. **51**: (No. 1). 1931.

An investigation was carried out on the physiological relations existing between the ovarian and hypophyseal hormones and the growth and secretory activity of the mammary glands. Guinea-pigs, rats and rabbits were employed in the various phases of the study. Attempts to induce mammary growth to the size characteristic of pregnancy by the administration of the follicular and lutein hormones were not successful. Administration of an extract of the anterior pituitary to immature animals previously treated with the lutein extract or to untreated adult females induced the growth of pregnancy and milk secretion. Further evidence is given in support of the idea that the ovarian hormones are necessary for mammary development to the pubertal condition. The lutein hormone may induce the early growth of pregnancy and apparently is necessary in preparing the glands for the action of the anterior-lobe hormone. To a greater or less degree, depending on the species, the ovaries are required to maintain the glands in the condition requisite for the pituitary stimulus. However, the profound growth of pregnancy, terminating in lactation, is apparently under the control of the anterior-lobe hormone or a substance physiologically similar. It is possible that there may be other factors, at present not understood, that are active in the regulation of this control. It is suggested that the placenta possibly is a factor therein concerned.

—Authors' Abst.

Histophysiology of hormone products. Pall, Wien. klin. Wchnschr. **43**: 573. 1930.

That the function of the pancreatic islets is connected with that of the adrenal medulla is demonstrated when on the injection of insulin, adrenalin is released into the blood stream. Similarly in regard to the ovary, ovarian extract injected into castrated females causes the return of the menstrual changes, and the chromaffin tissue in both sexes appeared to give an increased reaction. Ovarian extract appeared to influence the pancreatic islets morphologically and this may explain the disturbances in sugar metabolism in the pregnant female. The foregoing results are indicative of the close inter-relationship existing amongst the endocrine glands.—W. Susman.

Pathology of the thymus and thyroid gland during inanition (Pathologie der Thymus- und Schilddrüse bei Inanition). Stefko, W., Krankheitsforschung, **9**: 70. 1931.

Pathological-anatomical and clinical data on undernourished Russian children indicate that the endocrine disturbances are of primary importance. These disturbances appear within 4 or 5 years of chronic nutritional deficiency; they are more frequent in boys than in girls, and appear especially at the ages 8-9 and 12-13 years. The thymus presents degenerative changes in the medulla and Hassall's corpuscles; the lymphoid tissue is involved later. The thyroid gland undergoes follicular degeneration with colloid resorption and variable changes resembling struma diffusa parenchymatosa. Hypogenitalism is also characteristic. In general, the process of nutrition and especially the influence of vitamines affect the organism through the agency of the endocrine system.—C. M. Jackson.

Studies of the sexual cycle in birds. V. Effects of white light of different intensities upon the testis activities of the European starling (Sturnus vulgaris). Bissonnette, T. H., Physiol. Zool. **4**: (No. 4). 1931.

Under previously described uniform conditions, groups of starlings were subjected to light from 10-, 15-, 25-, 40-, 50-watt bulbs, and from 60-watt bulbs both with and without forced exercise, for equal periods nightly, from November 9th to January 27th. Controls received equal daylight periods only. Samples from all groups were killed for study on December 13th, 23rd, and January 27th. All except controls underwent progressive testis changes, leading to complete spermatogenesis in 44 days, and some birds, from even the 10-watt-treated groups, passed the climax of spermatogenesis before 79 days, even under increasing daylight periods after December 21st, and regressed to various degrees; others did not. Rate of acceleration of germ-cell activity increased with light intensity from 10- to 25- (perhaps 40) watt bulbs; but above that no constant differences resulted. Fifty-watt bulbs may be slightly more effective than 60's. Added exercise caused lag of onset of light-induced changes, both progressive and regressive. Data suggest a refractory period before appearance of light-induced effects, prolonged by added exercise, together with idiosyncrasies of susceptibility to regression. Juvenile birds gave neither so rapid nor so great increases in testis size and germ-cell activity as mature birds under like conditions. Total testis size, produced in midwinter by added electric light, sometimes surpasses the spring normal.—Author's Abst.

The process of sex transformation in parabiotic amblystoma. II. Transformation from male to female. Burns, R. K., Jr., J. Exper. Zool. **60**: (No. 3). 1931.

In 29 cases of male-female parabiotic Amblystoma tigrinum larvae, varying in age, five pairs show the gonads of the male in advanced stages of transformation to ovaries. This transformation is rendered possible by the existence in the young normal testis of a peripheral germinal layer, the male cortex, considered homologous with the true cortex of the ovary. In some cases this male cortex, stimulated by the hormones of the female partner, grows actively with concomitant regression of the medullary region of the gonad. This may result in a transformation so complete that large portions of the gonad are indistinguishable from normal ovary, while in other sections transformation is still in progress. The existence of the male cortex, with its latent physiological capacity, indicates that the early male gonad is a bisexual structure, with dual

capacity, enabling it to transform into an ovary under suitable conditions. However, transformation from male to female occurs only in a small minority of cases, while in all others the male dominates. Quantitative studies show that, where the female dominates, a large volumetric preponderance of the female gonads is always found, and is probably necessary. This preponderance is established early in development, and its origin may be fortuitous. The transformability of a testis may largely depend upon the relative amount of pre-existing male cortex.—Author's Abst.

Placental hormones. Collip, J. B., D. L. Thomson, J. S. L. Browne, M. K. McPhail and J. E. Williamson, Am. J. Physiol. **97**: 513. 1931.

Extracts prepared from fresh human placenta by extraction with one and one-eighth volumes of acetone have been separated into various fractions by the use of alcohol, ether and acetone, and these fractions have been studied both physiologically and chemically. As a result of a very large series of animal experiments, it may be concluded that at least three active substances are contained in the original acetone extract. The ether-soluble fraction has been shown to contain oestrin. After repeated extraction with ether from acid aqueous solution the aqueous phase has been shown to contain two oestrogenic substances. One of these is active when fed, the other only when injected. The former substance is effective in minute amounts when fed to immature female rats. Much larger doses may produce oestrus in adult castrates, but this may be due to traces of oestrin in such extracts. The latter, which is the anterior-pituitary-like hormone of the placenta, has been purified to a high degree and extensive observations have been made on its physiological effects.
—Authors' Abst.

Studies on the antagonism of follicular and luteal hormones (Recherches sur l'antagonisme des hormones folliculaire et lutéinique). Courrier, R., Compt. rend. Soc. de biol. **104**: 280. 1930.

The author concludes that a dose of folliculin sufficient to produce vaginal changes in a spayed guinea pig cannot evoke this reaction in a normal female in the presence of a young corpus luteum whose active condition is shown by the production of deciduomata. Larger and larger doses of folliculin in the presence of such an active corpus luteum render the decidual reaction progressively more feeble. The maximum effect is obtained when folliculin is injected early in the life of the corpus luteum and, in such cases, a reaction of the vaginal epithelium may occur. The folliculin affects the deciduomata indirectly through the corpus luteum.—J. C. D.

Properties of the comb growth promoting substance obtained from testes and urine. Dodds, E. C., A. Greenwood, H. Allan and E. J. Gallimore, Biochem. J. **24**: 1031. 1930.

From the benzene-soluble fraction after treatment by barium hydroxide was obtained a "water-soluble" fraction which contained the comb growth-stimulating activity. It is concluded that boiling N/10 acids and bases are not destructive, but that H_2O_2, pepsin HCl, and trypsin each destroy the activity. The "water-soluble" form when distilled at 0.1 mm. mercury pressure and 140-160° C. yields a potent, water-soluble, crystalline, oil-like distillate. A similar procedure applied to a petroleum ether-soluble fraction yielded a potent, dark oil which was insoluble in water.—F. C. Koch.

Relation of hysterectomy of long standing to voluntary activity in the white rat. Durrant, E. P., Am. J. Physiol. **97**: 519. 1931.

Thirteen hysterectomized and 11 control animals about 90 days old were kept in recording activity cages for 16 months. The uninterrupted rhythmic increase and decrease in voluntary activity, heretofore shown to be correlated with the oestrous cycle, indicate that the cyclic changes in the ovary of the white rat are independent of any hormonal influence from the uterus.
—Author's Abst.

Hormonal analysis of blood and urine of non-pregnant women after transfusion of blood from pregnant donors [Eine artefizielle Schwangerschaftsreaktion (A.Z.R.) bei der nichtschwangeren Frau, Beitrag zum Verhalten des Hypophysenvorderlappenhormons im nichtgraviden Organismus]. Erhardt, K., Deutsche med. Wchnschr. **56**: 1560. 1930.

From normal, pregnant donors 700 cc. of blood was transfused to each of five non-pregnant women with uterine hypoplasia, sterility, and amenorrhea of long duration. Blood withdrawn from the recipients as early as two hours and as late as 20 hours after the transfusion gave reactions II and III by the Zondek-Aschheim technique. Urine from these recipients as early as ten minutes, and as late as 22 hours after the transfusion gave reactions II and III. Urine samples obtained after 24 hours following the transfusion gave reaction I, or were completely negative. It is interesting to note that the transfusion led to no uterine growth, or alleviation of symptoms. From such data the author concludes that in non-pregnant women the excretion of hormones is essentially the same as in the pregnant woman.—M. H. Friedman.

Isolation of the male sexual hormone in crystal form, soluble in water (L'isolamento dell'ormone sessuale maschile in forma cristallizzata idrosolubile. Studio delle sue azioni fisiologiche). Frattini, B. and M. Maino, Archivo dello Istituto Biochimico Italiano, **2**: 639. 1930.

Previously in a critical review of the methods used thus far to isolate the male sexual hormone, the authors claim to have obtained a male sex hormone in pure crystalline form. To try its efficiency two tests only were considered as reliable, the seminal vesicle test, and the cock's comb test. Positive results in previously castrated rats were obtained in regard to the atrophied seminal vesicles which showed very well the four classic phases: increase in height of the epithelial cells; secretory activity with formation of granules; vacuoli and acidophylus secretion within the gland; more epithelial cells and cellular multiplication. The vesicles of control rats were in full involution. The Pézard capon comb test also was strongly positive. Owing to the similarity of the male sex hormone crystals and crystals of estrine, both substances were compared in similar tests. It was found that either one caused changes in the sexual tract, as well as some minor changes in the gonads, but in regard to the secondary characteristics the male hormone was required for male animals.
—G. V.

The calcium content of the serum of cattle with reference to the influence of the sexual organs (Der Serumkalkspiegel beim Rinde mit besonderer Berücksichtigung der Beziehungen zum Geschlechtsapparat). Frei, W. and M. A. Emmerson, Biochem. Ztschr. **226**: 355. 1930. Abst., Physiol. Absts. **16**: 202.

The calcium content of the serum of cattle in various stages of growth and of sexual condition has been examined. It is higher in calves than in the adult animal, and in female calves than in the male. In cows it is higher in the oestrus than in interoestrus and in pregnancy than in the non-pregnant state. Castration lowers it in males but raises it in females Cystic degeneration of the follicles of the ovary causes an increase, and the fluid from the cysts has a higher calcium content than has the serum. Injection of "progynone" reduces it, while that of "sistomensin" or of extract of the anterior lobe of the pituitary raises it. These variations of the serum calcium are largely controlled by the sympathetic-parasympathetic balance and the endocrine glands.

On the male hormone (Über Männliches Hormon). Freud, J., S. E. de Jongh, E. Laqueur and A. P. W. Münch, Klin. Wchnschr. **9**: 772. 1930.

Earlier negative results are considered as due to the use of too low dosages. The positive findings of McGee, Gallagher, and Koch on testis and those of Funk and Harrow on urine are confirmed. The hormone can be adsorbed from urine on charcoal and recovered therefrom by benzene and alcohol. The authors do not find the male hormone in female urine, but find the female hormone in testis tissue and male urine preparations. They could not confirm the sperm motility test of Moore and McGee, but did show the stimulating action of the hormone on seminal vesicle development in the castrated rat.

They report that the female hormone (menformon) acts as an "antimasculin" agent on the normal rat and cock, but not on the capon, hen or castrated rat. Menformon causes female feathering in both sexes and the male hormone causes comb growth in both hen and cock.—F. C. Koch.

Further studies on the mechanism of ovulation. Friedman, M. H., Am. J. Physiol. **97**: 520. 1931.

In a recent paper Hill and Parkes voice the opinion that the formation of a corpus luteum is the direct result of the act of ovulation itself, and "is not connected with the subsequent release from the anterior pituitary body of the stimulus to luteinization." In support of such hypothesis the authors recall the experiments of O'Donoghue, and of Ancel and Bouin, in which the artificial rupture of follicles in the rabbit is said to have led to the formation of corpora lutea. To test this hypothesis the experiments of O'Donoghue were repeated and extended. Through a flank incision under ether the right ovary of several rabbits was exposed and all the large follicles carefully punctured. After a varying period of time the ovaries were removed for examination. For controls against the factor of operative trauma, follicular puncture was performed on one ovary in each of several rabbits at varying intervals after coitus (five minutes to three hours). From such experiments it was found that: (1) follicular puncture in rabbits known to be in heat does not lead to the formation of corpora lutea; (2) follicles punctured in rabbits very shortly after coitus develop into normal corpora lutea indistinguishable from the corpora lutea in the ovary on the unoperated side. In further experiments it was found possible to produce corpora lutea in one ovary without affecting the ripe follicles in the contralateral ovary. This is achieved by the injection of a small quantity of an extract of urine of pregnancy directly into the follicles of one ovary. The corpora lutea so produced, however, are by no means entirely normal structures. Just how far these artificial corpora lutea deviate from the normal is at present under investigation.—Author's Abst.

Treatment of ovarian deficiency with ovarian extract (oestrin). Gardiner-Hill, H. and J. F. Smith, Lancet, **1**: 464. 1931.

The results of the treatments of 63 patients with varying grades of amenorrhea are detailed. Oestrin, standardized to contain 10 R. U./CC., was used; series of 1 cc. daily subcutaneously were given for 6, 12 or 18 days. The highest total number of units given a patient was 540 units. In primary amenorrhea the results were negative. In primary menstrual irregularity menstruation was regulated in 6 of the 19 patients. In secondary amenorrhea positive results were obtained in 20 of the 37 patients. In 12 of the successfully treated patients, subsequent menstrual rhythm was normal without any further treatment. In two of these patients, who were sterile, pregnancy subsequently occurred.—E. C. Hamblen.

Effects of injections of female sex hormone (oestrin) on conception and pregnancy in guinea pig. Kelly, G. L., Surg., Gynec. & Obst. **52**: 713. 1931.

It was found that small doses of female sex hormone injected for a period of several days into female guinea-pigs immediately after copulation will prevent conception in all cases in which an adequate dosage is used. The minimum dosage required is about 10 to 15 rat units. Interruption of pregnancy in this animal when about two weeks pregnant can be accomplished in practically all cases with a total dosage of 100 rat units. For animals pregnant about four weeks the gestation can be terminated by adequate dosage. An optimum amount for this stage is from 100 to 150 rat units. With much larger doses the pregnancy is usually terminated by abortion, but maternal mortality is high. In females pregnant from six to eight weeks, injections of doses varying from 300 to 1,150 rat units invariably bring an end to normal pregnancy and almost invariably cause the death of the mother. The death of the fetus after injections seems to be related to marked atrophic changes in the chorionic villi, resulting from pressure due to excessive hyperemia or other cause. The cause of death of the mother is problematic. The results with control animals indicate that the abortions and fetal deaths do not result from the injected material or from handling. Administration of as high as 600 rat units of estrin in six days to male and non-pregnant female guinea-pigs is not incom-

patible with the life and health of full-grown animals. The conclusion seems warranted that an excess of female sex hormone in the blood over the corpus luteum hormone is incompatible with conception and with continuance of normal pregnancy in the guinea-pig.—Author's Abst.

The critical intersexualities (Ueber die kritischen Intersexuellitäten). Marañon, G., Endokrinologie, **7**: 415. 1930.

Temporary states of intersexual conditions appear not unfrequently during puberty and climacteric periods. In boys there can be noticed during puberty comparatively frequently feminine traces: gynecomasty, accumulation of fat and delay of sexual development. Marañon calls this condition "prepuberal eunuchoid obesity." It is often combined with cryptorchism, lack of hair, mononucleosis, acrocyanosis. The body growth is generally normal. These boys are ordinarily bashful, they are sometimes particularly gifted for mathematics and music; their libido is weak and the appetite is generally strong. The basal metabolism is only slightly diminished, the intermediate carbohydrate metabolism is unaffected. Many of these cases undergo a perfectly normal development but in some the signs of hypogenitalism may remain. The prognosis is, therefore, uncertain during the prepuberal stage. The treatment with pituitary anterior lobe preparations is not very successful. Thyroid therapy is more effective. In girls there almost never occurs any outspoken masculinization during puberty even in cases of ovarian insufficiency except in rare pathological cases. Besides the well-known masculinization features in climacteric women there are some less familiar phenomena. The distribution of fat can become similar to that of elderly men and the voice becomes stronger. Occasionally there is an inclination toward male professions. Psychosexual inversions are not characteristic for the female climacterium, the normal libido frequently rather increases but Marañon interprets this fact as a sort of psychic masculinization. Men do not as a rule undergo any changes in the sense of feminization during their "climacterium." Similar features of intersexualism as the above mentioned have also been observed among animals. Sexual maturity occurs in men at a considerably later age than in women, but its duration is also longer in men. Marañon assumes that in each individual both sexes develop but at different times of life. In men the development of the female factor occurs, according to the above discussed facts, earlier than the full development of the male factor, hence the feminization during male puberty. In women, on the contrary, the persisting mature male factor becomes apparent after the expiration of the characteristics of female maturity. On the other hand, the earlier developed female factor in women covers the later developing male factor after female puberty. "Critical" conditions occur only when male characteristics are overcoming the female ones as during male puberty and during female climacterium but not during female puberty and male "climacterium." It seems that besides the sexual glands, the adrenals and the hypophysis also play a certain rôle in those conditions.—W. Raab.

Ovarian hormone and metabolism. McClendon, J. F., L. Myrick, C. Conklin and I. H. Wilson, Am. J. Physiol. **97**: 82. 1931.

We have studied the period between menstruations on the hypothesis that the changes are due to changes in concentration of hormone and find a slight rise in basal metabolic rate. Owing to the fact that this rise is less than the daily variations, a large number of determinations (342) had to be made in order to reduce the probable error. We found an increase in the volume of the nipples during the same period. Since it is well known that the endometrium increases during this period, it seems possible that the rise in basal metabolic rate may be due to the growth of tissue in the endometrium and mammary glands. As to what hormones are concerned with these changes, we have no data of our own except that the report by McClendon and Burr that injection of follicular hormone increased the basal metabolic rate of a woman lacking ovarian functions, was confirmed on another similar woman, but there was no quantitative relation between the amount of the hormone injected and the rise in B.M.R. It seems probable that a hormone from the corpus luteum causes the changes we have found, or that they are due to more than one hormone.—Authors' Abst.

Indications and technique for the sterilization of the woman—procedure. Biological methods. Laffont, A., Rev. franç. de gynecol. et d'obstet. **25**: 204. 1930.

These methods are not yet used in current medical practice. Temporary sterilization of laboratory animals has been obtained by subcutaneous injections of semen; ovarian grafts, administration of extracts of placenta and ovaries result in more or less prolonged sterilization. With these methods, interesting results have already been obtained in the human being. Folliculin, insulin, anterior pituitary extracts have also a sterilizing action on females, probably by different mechanisms. Vitamin E deficiency also results in the impossibility of fecundation of adult females. During the discussion of this report, Favreau expressed the opinion that research work on this line was dangerous and proposed to have it forbidden. The author protested energetically.—Z. M. Bacq.

On some fundamental laws of the dynamics of sex (Über einige Fundamentalgesetze der sexuellen Dynamik). Lipschütz, A., Arch. f. Frauenk. **16**: 199. 1930.

The law of follicular constancy and the law of puberty are discussed in view of the new statements on the hormone of the anterior lobe of the pituitary. —A. Lipschütz.

The follicular hormone (La Foliculina). Lipschütz, A., Rev. med. de Chile, **57**: 503. 1929.

This is a summary of the experimental work done with the follicular hormone since Allen and Doisy. The problems of the functional significance of the follicle and the corpus luteum are analyzed from a comparative point of view. No new experimental data are given.—Author's Abst.

New experiments on the transplantation of dried ovary (Neue Untersuchungen über Verpflanzung von getroknetem Eierstock). Lipschütz, A. and H. Kallas, Virchow's Arch. f. path. Anat. **277**: 694. 1930.

Desiccated ovaries were kept for 14 days on ice. Such an ovary is still able to recuperate endocrine activity when engrafted into the castrated animal, but survival is not more frequent as compared with those experiments in which the ovary had not been dried.—A. Lipschütz.

Oxygen use of the isolated ovary of the mammal (Über den Sauerstoffverbrauch des isolierten Säugetierovariums). Pflügers Arch. f. d. ges. Physiol. **223**: 56. 1929.

New observations on the metabolism of the isolated ovary (Nouvelles observations sur le métabolisme de l'ovaire isolé). Lipschütz, A. and S. Veshnjakov, Compt. rend. Soc. de biol. **100**: 982. 1929.

The oxygen consumption of the isolated ovary of the glinea-pig has been studied under different experimental conditions. There is an oxygen consumption for several days at temperatures lower than 38°, even on ice. The difference between oxygen use at various temperatures is $Q_{10}=2.5$, in such a manner that oxygen use on ice is about 1/20 to 1/40 that at body temperature. Oxygen use per mgm. is about one-third of that in the mouse. The law of "liminal thickness" of Warburg has to be taken into consideration when the maximal oxygen use of ovary is considered. The better results with transplantation of isolated ovaries after keeping on ice can be explained on the assumption that oxygen use being highly reduced at low temperature, the thickness of the ovary is not greater than corresponds to the liminal thickness at this low temperature. The possibilities of keeping an isolated organ for transplantation in good condition will probably be augmented if the organ is kept on ice in an atmosphere of oxygen; under these conditions the liminal thickness of the guinea-pig ovary is about 3.5 mm. It might not be excluded that the liminal thickness will be greater in the woman; this depends entirely upon whether the intensity of respiration in the ovary of the woman is smaller or not than in the guinea-pig. If the isolated ovary has been kept at temperatures lower than 0°, there is an oxygen use when examined afterwards at

about 18°; but it diminishes rapidly during 24 hours. At body temperature such an ovary shows oxygen use only during a quarter of an hour. By these observations it is explained why an ovary which has been kept at temperatures lower than 0° never takes when engrafted, whereas ovaries kept for 2 weeks on ice or even at temperatures of about 15 to 20° can take and recuperate follicular development and endocrine function. The same phenomena as observed in the ovary exposed to temperatures lower than 0° are shown by triturated ovaries. When the oxygen use of the pulp is studied, there is in the first 30 minutes an oxygen use averaging about half the normal, but in the next 30 minutes there is no more oxygen use. Freezing of the ovary is by this demonstrated as being identical with mechanical destruction of the organ.
—A. Lipschütz.

Action of serum from a male animal on combs of capons. Notes on limitations of "all or none law" (Action du sérum d'animaux de sexe masculin, sur la crête du chapon. Restrictions a apporter a la loi du "tout ou rien"). Parhon, C. I., L. Ballif and A. Stirbu, Compt. rend. Soc. de biol. **104**: 218. 1930.

Two capons received subcutaneously daily doses of serum from an eight-year-old stallion. After 34 days no signs of masculinization appeared. Numerous untreated capons showed spontaneous recovery of their male characteristics. In these, testicular tissue was invariably found. There seemed a relation between the amount of testicular material and the degree of masculinity. This is not according to the "all or none" law.—J. C. D.

Vital function studies. VIII. Weight calculation in pregnancy. Rowe, A. W., J. Lab. & Clin. Med. **16**: 874. 1931.

Groups of pregnant women, maintained under divergent domiciliary conditions, have been studied continuously during both the ante- and post-partum periods. Increments in weight and other simple physical measurements antepartum, and decrements after delivery have been recorded. As earlier noted, the sitting height in the recumbent female can be approximated by adding 1.1 cm. to the distance between the perineum and vertex, as measured with special calipers. The hip circumference in a recumbent position during pregnancy averages 0.7 cm. less than in a standing posture; the difference averages 0.4 cm. after delivery. Similar comparisons show that the recumbent chest measure averages 0.8 cm. more than that of a standing pregnant subject; the difference is 0.5 cm. after confinement. The actual weight of the recumbent pregnant woman may be calculated with reasonable accuracy in the majority of cases either: (a) by adding 5 per cent to the prediction of the hip formula, or (b) computing the algebraic mean of the predictions respectively from Dreyer's sitting height ("trunk") and chest formulas.—Author's Summary.

Iritis and menstruation. Considerations concerning the relation of endocrine secretions (Iritis und Menstruation Betrachtungen über innersecretorisch Zusammenhänge). Thies, O., Arch. f. Ophth. **124**: 103. 1930.

The author reviews the literature on the subject of diseases of the eye and and their connection with changes in other individual organs of the body. Various authors are cited whose work has contributed valuable observations along these lines. Among these are references to diseases of the iris that occasionally are brought on by diabetes, diseases of the visual pathway as are observed, not infrequently in pregnancy and the lactation period, less often at the menstrual period, and diseases of the cornea that frequently show a more degenerate nature. A group of authorities believe that lens changes are of an endocrine nature and that the senile cataract is an accompaniment of the atrophy of the sex glands in senility. The conclusion is drawn that one may seek in the different developments of glandular activity for a substantial factor in the origin of pathological increase of intraocular pressure. Case reports of different workers are cited, especially a case of recurrent amblyopia at menstruation, that in a young girl, which appeared during three consecutive menstrual periods; recurrent hemorrhages into the vitreous that occurred in the same connection; and a number of reports which indicate a connection between certain cases of iritis and menstruation. The author believes that practically every ophthalmologist has had a number of cases in practice, of eye disturb-

ances that have definite connections with disturbances of the female sex life. He recalls several cases from his own practice, showing always in the usual rotation of recurrent phlyctenules and infiltrate, some so-called vicarious bleeding into the vitreous, optic neuritis, macular disturbances with excessive myopia, and most severe cases of iridocyclitis, in the climacteric period, which frequently came for treatment first, with a secluded pupil. He discusses at length, three cases of iritis, because of their connection with menstruation, and concludes that in these three cases there was an endocrine dysfunction, more specifically, a deficient hormone activity of the ovaries, as a causative factor. To successfully combat these rare cases of eye disease, therapy must be built along the endocrine therapeutic lines and work must be conducted in close collaboration with a gynaecologist skilled in endocrine questions.
—J. P. Johns.

The effect of the estrus producing hormone on the growth of the mammary gland. Turner, C. W. and A. H. Frank, University of Missouri Agricultural Experiment Station Research Bulletin, **145**: 5. 1930.

As a result of previous work indicating that the rate of excretion of the estrus producing hormone in the urine of pregnant cattle increases during the course of gestation, a study was made of the effect of the hormone on the growth of the mammary gland in the rabbit. In the normal rabbit after continued estrus, the mammary glands show extreme extension of the duct systems resembling the naked branches of a tree. If pregnancy or even pseudo-pregnancy now ensues, the ducts develop lobules containing large numbers of alveoli, resembling the budding of leaves from the smaller branches. It was found that the daily injection of 20 rat units of the estrus producing hormone, recovered from pregnant cow's urine, for 30 days in male castrate rabbits and in female rabbits castrated previous to puberty, caused the growth of the duct system of the glands equal to that produced during continued estrus in the normal female. The results obtained seem to warrant the conclusions that the estrus producing hormone will cause the growth of the ducts equal to that produced during estrus, that the rate of development is not hastened by increasing the dosage, and that there was present in none of the oils used a hormone or hormones which would produce the type of growth characteristic of pregnancy.—C. W. Turner.

A study of the estrus producing hormone in the urine of cattle during pregnancy. Turner, C. W., A. H. Frank, C. H. Lomas and C. W. Nibler, University of Missouri Agricultural Experiment Station Research Bulletin, 150. 1930.

In a study of the rate of secretion of the estrus producing hormone in the urine of pregnant cows, considerable variation was observed at all stages of gestation. On the average, however, the hormone was found to be secreted at a low level during the early stages of pregnancy then gradually increased until the time of parturition. Following parturition the secretion of the hormone declined rapidly. Of the animals included, little difference was found in the rate of secretion of the hormone by Holstein and Jersey cattle. However, in comparison with beef cattle it was found that the former begin to show a very noticeably higher level of secretion after 100 days of gestation. In view of the experimental work indicating that the estrus producing hormone plays a part in the normal growth of the mammary gland, reasons are advanced for the belief that the increasing secretion of the hormone during pregnancy is required for the development of the gland.—C. W. Turner.

The relation between the estrus producing hormone and a corpus luteum extract on the growth of the mammary gland. Turner, C. W. and A. H. Frank, Science, **73**: 295. 1931.

Mammary gland development similar to that characteristic of pregnancy was induced in castrated male and female rabbits by the simultaneous injection of a corpus luteum extract and the estrus producing hormone. One cc. of a crude corpus luteum extract was injected simultaneously with 12 r. u. of estrus producing hormone daily for 30 days. Milk secretion was not observed.
—C. W. Turner.

The occurrence of the Abderhalden reaction after parenteral administration of the hypophysis preparation prehormone and of the ovarian hormone folliculin (menformone) (Weitere Studien über das Wesen der der Abderhaldenschen Reaktion zu Grunde liegenden Vorgänge). Abderhalden, E. and S. Buadze, Fermentforsch. **12**: 262. 1930. Abst., Chem. Absts. **25**: 730.

Subcutaneous injection of prehormone and menformone in castrated or non-castrated dogs of either sex results in a positive Abderhalden reaction of the urine toward ovarian, testicular and anterior hypophysis substrates. The hormone preparations themselves contained no specific enzymes and no appreciable quantities of protein. It is suggested that a part of the hormones occurs as a structural unit of proteins and becomes available when occasion arises. Possibly the hypophysis and the sex glands contain proteins which have structural features in common. In the absence of sex glands the specific unit would then be supplied by the hypophysis. As a practical application of these observations the fact is pointed out that glandular therapy of the patient must be taken into account when interpreting a positive diagnosis by the Abderhalden reaction.

Gynecomastia. Cheifitz, A. B., Vrach. dielo, **14**: 333. 1931. Abst., J. A. M. A. **97**: 1188.

Cheifitz finds 164 instances of gynecomastia in the literature, five from his own experience. Histologically, the author believes this a fibro-adenomatous condition of the male mammary glands. The condition may be another instance of sexual irregularity governed by adenoma of the hypophysis. The author advises operation.

Ossification in the absence of the parathyroid glands. Dragstedt, C. A., Am. J. Physiol. **97**: 517. 1931.

Experiments have been performed showing that bone repair after thyroparathyroidectomy in dogs is delayed, confirming the reports of many investigators in this respect. Bone repair goes on to completion, however, and the delay becomes significantly less if calcium administration is adequate, indicating that the parathyroid hormone is not indispensable for the processes of ossification. This is more clearly indicated in experiments on ectopic bone formation. Bone will form in fascial transplants in the wall of the urinary bladder in thyroparathyroidectomized dogs if adequate calcium is given, while it does not form if such dogs are maintained with low blood calcium levels.
—Author's Abst.

Note on the follicular hemorrhages in the Aschheim-Zondek reaction (Sur les hémorragies folliculaires dans la réaction d'Aschheim-Zondek).

On the Aschheim-Zondek reaction (Sur la réaction d'Aschheim-Zondek). Emanuel, S., Compt. rend. Soc. de biol. **104**: 495; 497. 1930.

Follicular haemorrhages are not a direct result of the hormonal action of the anterior lobe. Its effect is to mature the follicle and initiate its change into the corpus luteum. During these processes there is an intense hyperemia, which under certain conditions results in rupture of the capillaries and production of the characteristic haemorrhagic spots. Grafts of entire adult rat hypophysis into 17 mice resulted in a marked maturing of the follicles but not in the appearance of corpora lutea. This indicates that the two processes are controlled by separate hormones.—J. C. D.

The diagnosis of pregnancy by the Aschheim-Zondek test. Ettinger, G. H., G. L. M. Smith and E. W. McHenry, Canad. M. A. J. **24**: 491. 1931.

The authors report results of examination of urines from 112 cases in which pregnancy was suspected, and from 25 controls, with the diagnosis confirmed in every case. Included among the positive diagnoses were two cases of ectopic pregnancy, one of hydatidiform mole and three of incomplete abortion. The mouse test was used. One mouse was examined on the fourth day; if the ovaries showed the blood spots the diagnosis was made immediately; otherwise it was delayed until the fifth day, when the other mice were examined. If the diagnosis was required in a shorter time, the rabbit test introduced by Friedman was used. The bromine water test of Voge was attempted with 57 specimens of urine. The results showed a 25% error.—G. H. Ettinger.

Hyperplasia of the endometrium and the hormones of the anterior hypophysis and the ovaries. Fluhmann, C. F., Surg. Gynec. Obst. **52**: 1051. 1931.

Hyperplasia endometrii is the name given to a characteristic lesion of the endometrium which should not be considered as a purely local change but as part of a definite clinico-pathological entity. It was found in 2.8% of the last 1,700 hospital admissions on the Stanford Gynecological service, and accounted for 12.2% of patients in a series of 507 women with abnormal uterine hemorrhage. It may occur at any time during the active sexual life of women and has been observed in the postclimacteric period, but the majority of cases are found just before and during the menopause. Approximately 75% of the patients were multiparae. The outstanding symptom of the disease is uterine hemorrhage, which is manifested mainly in two ways: (1) Periods of profuse bleeding occurring at cyclic intervals, and (2) prolonged, continuous or intermittent, hemorrhages. No relation between hyperplasia and endometrii and systemic disease was established, but in about 30% of the cases there was an associated pelvic condition. The endometrium is characterized by a marked hyperplasia of both glands and stroma. There is an absence of the corresponding cyclical changes of menstruation and a disorderly arrangement of the glands, of which 3 main types are seen: (1) glands lined by a single layer of cylindrical epithelium; (2) cystic glands with a low cuboidal epithelium; and (3) glands with a stratification of the cylindrical epithelium. In specimens obtained at the time a patient is bleeding may be seen in addition areas of necrosis, thrombosis of blood vessels, and infiltration with leucocytes and lymphocytes. Epidermidalization is occasionally noted and may give rise to confusion with carcinomatous changes. A co-existence with carcinoma has been described. The ovaries of patients with hyperplasia endometrii characteristically show the presence of cystic ripening follicles, atretic follicles, and theca lutein cysts, and there is an absence of mature corpora lutea. A number of cases with ovarian new-growths have previously been described, and one additional instance of granulosa cell carcinoma is herein reported. Functional studies have demonstrated an excessive production of oestrin during the course of this disease, and the name "hyperoestrinism" is suggested to describe this condition. In only one case out of 10 was it possible to find large amounts of the anterior puititary sex hormone in the blood. Evidence is advanced suggesting that hyperplasia endometrii is the direct result of an overstimulation of the endometrium by oestrin and the complete absence of progestin influence. The chief local factor producing hemorrhage is the occurrence of areas of tissue disintegration. Two possibilities regarding the induction of necrosis in the endometrium have been discussed, namely: (1) a sudden cessation of oestrin production, such as would occur consequent to the death of the ovum and atrophy of the follicle; and (2) a prolonged excessive oestrin stimulation such as would result from the persistence of cystic ripe follicles. The etiology of this disease is as yet obscure but it is evidently the result of an endocrine disorder rather than a local pelvic condition. The possible involvement of the anterior hypophysis is considered. The use of repeated curettages in younger patients and intra-uterine radium applications for women of the menopausal age are recommended as the most satisfactory methods of treatment evolved to date.—Author's Abst.

Experimental studies concerning the role of the hypophysis in water metabolism (Experimentelle Beitrage zur Rolle der Hypophyse im Wasserstoffwechsel). Goldzieher, M. and J. Kaldor, Ztschr. f. d. ges. exper. Med. **76**: 819. 1931.

The authors injected diuretics in guinea pigs and found cellular changes in the tissue of the anterior lobe with an increase in the number of basophilic and a decrease in the number of eosinophilic cells just before the increased urine output was manifest. When the diuresis was over the microscopical changes in the anterior lobe disappeared. The authors conclude that the microscopical picture is related to the primary secretion of a specific diuretic hormone by the anterior lobe. In further experiments they investigated the influence of pituitrin upon the water excretion in india ink treated animals. The effect of the injection alone was an increase of water output, which, after the medication with pituitrin, was enormously augmentated. But the effect of pituitrin was opposite when novasurol was given: the diuresis was less effective, if the reticulo-endothelial system was blocked with india ink. The individual effect of the hormones of the posterior lobe upon the body tissue and the reticulo-endothelial system is discussed.—R. Engel

Cases of Simonds disease. Graham, D. A. L. and R. F. Farquharson, Proc. Am. Assoc. Physicians. Abst., J. A. M. A. **96**: 1987. 1931.

A woman, aged 46, was admitted to the hospital, and died without coming out of coma. The history obtained after death showed that the patient had been healthy until eleven years before, when after birth of her fifth child she had puerperal sepsis. She was weak, could not work, and menstruation never returned. Her hair became gray and coarse, the face was wrinkled, and there was extreme muscular weakness and loss of weight. Autopsy showed a smallness of all the organs of the body and complete depression of the anterior lobe of the hypophysis. There were but few remnants of this tissue, it being mostly replaced by connective tissue. Simonds considered that these cases were due to septic emboli followed by destruction of the anterior lobe of the pituitary. He called the condition hypophyseal cachexia. Three of our cases followed puerperal sepsis in women. One case, in a male, showed a four plus Wassermann reaction and autopsy showed fibrosis of the pituitary body. Patients all manifested sensitiveness to cold, lowered metabolic rate, lethargy, somnolence, weakness, forgetfulness and mental changes, with discovery at autopsy of general smallness of the organs. The features showed marked premature senility.

The follicle-stimulated effect of pig anterior lobe on the monkey ovary. Hartman, C. G. and R. R. Squier, Anat. Rec. **50**: (No. 3). 1931.

This paper reports the histological findings in a monkey exhibiting the Smith-Engle phenomenon (growth of follicles) in response to implantation of fresh anterior-pituitary substance (preliminary report in Proc. Soc. Exper. Biol. and Med. **27**: 338. 1930). Two glands from castrated male pigs were implanted on each of four successive days and the animal killed with gas six days after the last implant. Excessive congestion characterized both uterus and ovaries. The latter were enlarged ten- to fifteen-fold over the size found at laparotomy when the experiment began; the increase was due to growth of an enormous number of graafian follicles which were all mildly atretic. There was no luteinization and only one blood follicle (therefore, no "Prolan B" or "Prolan C" effect). The uterus was in the midinterval stage. Six photographs illustrate the paper.—C. G. Hartman.

Studies on the pituitary. VII. The separate identity of the pressor and melanophore principles. Hogben, L. and C. Gordon, J. Exper. Biol. **7**: 286. 1930.

When pituitary extracts are subjected to prolonged action of sodium hydroxide above normal concentration the destruction of pressor activity is accompanied by an appreciable increase in melanophore activity. The increase in melanophore activity is easily explicable, because constriction of the vessels by the pressor component would tend to mask the activity of the melanophore stimulant. There is thus adequate proof for the view that the melanophore, pressor and oxytocic activities of pituitary extracts are referable to distinct entities. In using the term entity one must not eliminate the possibility that these three activities are referable to different radicles in the same molecule, since the experimental results are not incompatible with the view that the separation of the three activities involves the fragmentation of a complex molecule. In the absence of direct evidence for this alternative, it is an economy of hypothesis to conclude that three separate autacoids exist in the gland.
—Authors' Summary.

Diabetogenic substance of the anterior pituitary (Sobre la substancia hipofisaria que refuerza la diabetes pancreática). Houssay, B. A. and A. Biassotti, Rev. Soc. argent. de biol. **7**: 3. 1931.

Hypophysectomy antagonises the appearance of pancreatic diabetes in toads; subcutaneous implantation of one or two glandular lobes (anterior lobe of mammals) is followed by an intense diabetes. The intermediate-neural lobe (posterior lobe of mammals) is less active and all other organs of the toad tested were inactive. This same activity was found in the anterior pituitary of fishes, batrachians, birds and mammals, including man. The anterior lobe kept in acetone maintains its activity. The active principle is soluble in water and alcohol 60°, insoluble in absolute alcohol, ether, acetone, chloroform and

benzene; it is destroyed at 100°C, does not pass the ultrafilter and is easily adsorbed. It differs from the principle with sexual activity in that it is equally active in all species whatever its origin.—J. T. Lewis.

Oral administration of anterior pituitary substance (Die Perorale des Hypophysenvorderlappens). Janssen, S. and A. Loeser, Klin. Wchnschr. **14**: 649. 1931.

The authors were able to establish sexual function in infantile rats by oral administration of powdered anterior pituitary extract over a period of 28 days. Twelve rats weighing 20-30 grams were fed 3½ grams of dry powdered acetone extract of anterior pituitary gland daily. After 17 days 5 rats showed proestrus, after 28 days 6 showed estrus and the rest proestrus. Twelve rats were kept as controls. On the 28th day a section of the ovaries showed enlarged follicles in all test animals and corpus luteum in but three of these. Only one of the control animals showed spontaneous estrus and corpus luteum on examination.—B. Parvey.

The site of formation of the "anterior pituitary" hormone in pregnancy (Die Bildungsstätte des "Hypophysenvorderlappenhormons" in der Gravidität). Philipp, E., Zentralbl. f. Gynäk. **54**: 1858. 1930.

Sixteen samples of human anterior pituitary tissue, implanted into immature female mice, caused follicular haemorrhages and formation of corpora lutea. The results were independent of the age or sex of the donors, and were positive also from cases of primary amenorrhoea of long standing. In contrast to this, 11 samples of anterior pituitary tissue from pregnant or parturient women were completely negative. Fourteen samples from new-born infants and foetuses were negative or at most caused some enlargement of follicles and premature oestrus. The author concludes that the "anterior pituitary" hormone of pregnancy urine is formed not in the pituitary but in the placenta. Implants of placenta or of the mucosa of pregnant uteri have the same effect as implants of normal anterior pituitary, except that ovulation was never observed with the former. The amount of hormone in the placenta is greatest in early pregnancy.—D. L. Thomson.

Chemistry of the sex hormone of the anterior lobe of the pituitary gland (Zur Chemie des Hypophysenvorderlappen-Sexualhormons). Reiss, M. and F. Haurowitz, Ztschr. f. d. ges. exper. Med. **68**: 371. 1929.

Preparations from beef pituitary glands and those from urine of pregnant women showed similar chemical behavior and therefore the active principle of each is probably the same. Both are inactivated by the protein, peptone and polypeptide splitting enzymes, trypsin and papain KCN also by the specifically peptone splitting enzyme of Jack bean meal. Papain without KCN is only protein splitting and does not affect the hormone. Therefore the hormone must be closely related to peptones. The inefficiency of oral administration of active preparations is thus clear. In harmony with this view of its chemical nature are the facts that fairly pure fractions are not precipitated by protein precipitants such as sulfosalicylic acid, are dialyzable and give the biuret and various amino acid tests. It is adsorbed on the precipitates with alumina gel and uranyl acetate and may be eluted with weak ammoniacal solutions. Use of its adsorption behavior is made in the purification process. The hormone is destroyed by 1% hydrogen peroxide, only partly by benzoyl chloride and not at all by a stream of oxygen or by shaking with dimethyl sulfate. It loses much of its activity on standing for months.—N. K. Schaffer.

Concerning the luteinizing principle of the anterior lobe of the hypophysis (Über den luteinisierenden Wirkstoff des Hypophysenvorderlappens). Reiss, M., H. Swlye and J. Balint, Endokrinologie, **8**: 259. 1931.

The luteinizing hormone, free from the growth hormone, was prepared in a stable powder form from alkaline extracts of the anterior lobe of the hypophysis. It showed no loss of activity after standing for eight months. When injected into rats it produced completely luteinized ovaries, but no permanent injury to these organs. This extract is indicated, for clinical trial, in cases of uterine haemorrhage of ovarian origin.—E. S. Young.

Response of the male genital system of the immature domestic duck to injections of anterior-pituitary substances. Schockaert, J. A., Anat. Rec. **50**: (No. 4). 1931.

The influence of various anterior-pituitary substances upon the development of the reproductive system, the onset of spermatogenesis, and the formation of mature spermatozoa was studied in young ducks. In contrast to rats and mice, which become mature at the age of six to eight weeks, ducks do not show any signs of spermatogenesis before four months. In ducks only 50 days old, complete spermatogenesis with living spermatozoa has been induced after two weeks of daily injection of a fresh beef anterior-lobe suspension. At the same time, the testes enlarge markedly, an enlargement of some forty times the relative weight of the control testes having been observed. A purified growth hormone (phyone) showed a similar, but less effective, action on the growth of the testes and the spermatogenesis, while even higher dosages of a luteinizing hormone and prolan were practically without effect. In some instances destructive changes in the dividing germinal epithelium were found, but are not considered as due to a specific action of the pituitary hormone. The penis remained entirely immature. The two possible explanations of this dissociation between the responses of the germinative epithelium and the secondary reproductive organ are discussed.—Author's Abst.

Biedl's disease (Biedlsche Krankheit). Serejski, M. J., Med. Klinik. **25**: 1620. 1929.

The author reported a case of Laurence-Biedl Syndrome under the title of Biedlsche Krankheit on the occasion of Biedl's sixtieth birthday anniversary. The family history was negative. The mother gave birth to 5 children, 3 of whom died in infancy. One sister who survived was normal. The patient was a female 27 years old. She was born at full term, was delivered instrumentally and was traumatized at birth which produced a swelling on the left side of the skull which lasted 4 years. She was born with 6 fingers on the left hand and 6 toes on the left foot. She walked at 9 months but did not talk until she was 4 years old. Dentition was normal. She was obese from childhood. At the age of 8 she entered school and progressed slowly for 2 years when she discontinued. Menstruation began at the age of 13. She developed night blindness when she was 8 years old. This was followed by optic atrophy, retinitis pigmentosa and hemeralopia. Speech was defective. She was mentally deficient and her mental age was rated as 6 according to the Binet-Simon test. She was an imbecile, bordering on idiocy. The blood Wassermann reaction was negative. The case exhibited all the characteristic symptoms of the Laurence-Biedl syndrome with the exception of hypogenitalism. In this respect her case resembled one reported by Curshmann and Deusch.—H. G. Beck.

The relative increase in metabolism of the liver and of other tissues during protein metabolism in the rat. Dock, W., Am. J. Physiol. **97**: 117. 1931.

The rate of oxygen consumption of rats, fed on a diet containing 74% casein and anesthetized with chloretone, was compared with that of controls fed on a diet containing no casein, immediately before and after ligating the blood supply of various regions of the body. The O_2 consumption of the kidneys, in terms of O_2 per minute per 100 sq. cm. of body surface, was practically the same in the rats on high and in those on low protein intake, although the total O_2 intake of the former group was 35% greater than the controls on low protein. Urinary secretion was not measured and no conclusions as to renal metabolism are to be drawn from these observations. The O_2 consumption of the hind-quarters was only 8% greater in the rats on the high protein diet, while that of the abdominal viscera was 141% greater during protein than during carbohydrate feeding. At least 85% of the heat evolved as a result of the specific dynamic action of protein in chloretone-anesthetized rats is liberated in the abdominal viscera. The significance of these facts is discussed in the light of previous observations by other workers and it is concluded that the liver is probably the chief site, and possibly the only site, of the intermediary metabolism of those amino-acids which raise the metabolic rate, and that at least 80% of the specific dynamic action of these acids is due to the increased energy liberated by the hepatic cells during protein digestion.
—Author's Abst.

The formation of fat from carbohydrates under the influence of insulin. Bürger, M. and W. Rückert, Ztschr, f. physiol. Chem. **196**: 169. 1931. Abst., Chem. Abst. **25**: 3702.

To determine the effect of insulin on fat metabolism, 2 milk goats on a constant ration were subjected to alternate 3-day periods with and without insulin injections. The milk was analyzed daily and daily determinations were made of the animals' blood sugar. Insulin caused a moderate decrease in the volume of milk, but an increase in the caloric value represented by the sum of the fat, carbohydrate and protein calories. This increase in caloric value was due essentially to increase in fat content. In the normal animals the blood sugar varied between 70 and 54 mgm.%. Under insulin treatment the blood sugar reached a value as low as 24 mgm.% without any "hypoglucemic symptoms" in the animals. The residual nitrogen of the milk varied within the narrow limits of 56 and 67 mgm.%; with insulin it reached 80 mgm.%. The freezing point of the normal milk varied between 0.59° and 0.63°, while that of the insulin milk was 0.57° and 0.60°. When 150 grams of glucose was administered orally to the fasting animal during a period of hourly milking, the yield of milk fat increased six-fold in the next milking as compared to the previous hourly average. This striking result is interpreted as a conversion of carbohydrate into fat.

Influence of acetyl-choline on insulinemia (Influenza dell'acetilcolina sull'insulinemia). Condorelli, F., Boll. d. Soc. ital. di biol. sper. **5**: 977. 1930.

The administration of moderate doses of acetyl choline to rabbits caused a decrease in the amount of insulin, or insulin-like substances which could be extracted from the blood. The administration of adrenalin, on the other hand, caused an increase in these substances.—G. V.

The effect of insulin upon the sympathetic nervous system. Danilevskii, B. and P. A. Wyalkova, Arch. f. exper. Path. u. Pharmakol. **159**: 275. 1931. Abst., Chem. Absts. **25**: 4052.

Intravenous injections of insulin cause a decreased response to faradic stimulation of the smooth muscle which retracts the third eyelid of the cat, i. e., it depresses the excitability of the sympathetic motor nerve and nerve endings. This effect is increased by the simultaneous injection of alkalies, and lasts 30-40 minutes, the recovery being hastened by adrenaline. Calcium chlorid given intravenously suppresses this insulin effect; potassium chlorid strengthens it.

Secondary alterations in total serum calcium after the administration of glucose and insulin. Ellsworth, R., J. Clin. Investigation, **8**: 139. 1929-30.

The administration of glucose and insulin to six normal individuals, one diabetic patient and one patient with general paresis resulted in a prompt fall of phosphorus as shown formerly by Benedict and Harrop. There was a definite tendency for the total serum to rise. The first rise in calcium was usually observed in the same hour as the first fall in phosphorus—the changes gave the appearance of being synchronous. Both the phosphorus and calcium effects were seen to have disappeared usually at the end of four hours.
—Author's Summary.

A pancreatic circulatory hormone (Über eine neue innersekretorische Funktion des Pankreas. V. Mitteilung: Über ein Kreislaufhormon). Frey, E. K., H. Kraut and F. Schultz, Arch. f. exper. Path. u. Pharmakol. **158**: 334. 1930. Abst., Physiol. Absts. **16**: 192.

Large amounts of an active circulatory hormone are present in normal pancreas and in the fluid from pancreatic cysts. The material prepared from the pancreas is identical with that previously reported in the urine. Kallikrein, as the authors name the substance, is chemically and pharmacologically sharply differentiated from insulin, but has functional relations with this other internal secretion. The spleen has some indirect effect on the amount of the hormone present.

Studies in carbohydrate metabolism. II. Glucose-lactic acid cycle in diabetes. Himwich, H. E., W. H. Chambers, Y. D. Koskoff and L. H. Nahum, J. Biol. Chem. **90:** 417. 1931.

Twenty-two observations were made on nine depancreatized dogs, and eight observations on five phlorhizinized dogs. They all indicate, especially those on depancreatized dogs, that lactic acid is liberated by muscle and removed chiefly by liver, while glucose is poured out by the liver to be absorbed by muscle and other tissues or excreted. Thus the glucose-lactic acid cycle between muscle and liver functions in diabetes just as it does under normal conditions. It is clearly demonstrated that by means of this mechanism, lactic acid, a waste product of muscular activity, is converted into a precursor of the glucose of the blood, accounting in the present experiments for approximately 0.4 of the glucose released by the liver.—H. E. Himwich.

Physiological studies on insulin. Memoir II. Hyperglycemic action of blood of the diabetic dog. (Études physiologiques sur l'insuline IIe Memoire. Action hyperglycemiante du sang de chien diabetique). Képinov, L. and S. Petit-Dutaillis, Arch. internat. physiol. **34:** 58. 1931.

Blood in amounts from 400-500 cc. was transfused from a depancreatized dog to a normal dog. This transfusion caused a primary rise of blood sugar in the recipient which was followed by a fall. There was, however, a secondary rise of blood sugar in the recipient between the fifth and eighth hours after the transfusion. When the blood from a normal dog was transfused into a normal dog there was no appreciable effect on the blood sugar. The injection of glucose did not cause a secondary rise of blood sugar. When the blood of a depancreatized dog having a normal blood sugar due to insulin treatment is transfused into a normal dog, the blood sugar of the recipient will rise. The purified dialysate from the blood of a depancreatized dog will cause a similar effect upon injection. The dialysate of normal blood will not affect the blood sugar. From their results the authors conclude that in diabetes there is a substance present in the blood which is capable of producing hyperglycemia.
—E. L.

Treatment of diabetes mellitus in the presence of other acute febrile diseases. Mayer, L. H. Jr., Pennsylvania M. J. **34:** 363. 1931.

Acute febrile diseases in the diabetic child will be encountered more frequently as the expectancy of life increases. During an acute febrile disease, diabetes invariably becomes worse. Glycosuria and acidosis always occur. Diabetic children withstand infections better if the fatty acid glucose ratio of the diet has been kept at less than 1.5 to 1. With proper adjustment of diet and suitable dosage of insulin, diabetic children are able to resist infections. The lowered carbohydrate tolerance encountered in febrile diseases is temporary. Recovery to the former level is the rule. Insulin should be given by the hour and not by the day.—I. B.

Diabetes mellitus; sugar consumption in its etiology. Mills, C. A., Arch. Int. Med. **46:** 582. 1930.

The author attempted to discover whether any relationship holds between sugar consumption and the diabetes death rate. Annual per capita consumption of sugar was obtained for the countries of the world and comparison made with the diabetes death rate in these countries. No constant relationship was found, although of the 13 countries highest in sugar consumption, 11 were among the 13 highest in diabetes death rate. In many instances an increasing diabetes death rate has been accompanied by declining sugar consumption, and vice versa. The author concludes that sugar consumption is not related in a causal way to the death rate from diabetes.—Author's Abst.

Diabetes mellitus and its complications. An analysis of 827 cases. Murphy, F. D. and G. F. Moxon, Am. J. M. Sc. **182:** 301. 1931.

In the cases reviewed, only 17.6% were without complications. Of the 681 cases in which there were one or more associated diseases, 69.2% died. From their cases, the authors feel that early recognition and treatment of all complications should be one of the most important aims in diabetic treatment.
—E. L.

A study of five hundred diabetics. Sevringhaus, E. L., Am. J. M. Sc. **182:** 311. 1931.

Following the diet plan using the Woodyatt type of ratios of fat, protein and carbohydrate to give a maintenance diet (with insulin if necessary), 59.8% of the patients discharged from the hospital required insulin. Of the 90 deaths in this series, the causes were as follows: neglect 10, coma 11, cardio-vascular renal disease 20, carcinoma 3, pneumonia 16, tuberculosis 4, and post gangrenous condition 15. A large number of the patients had pains in the lower extremities. The visual function of 38% showed a marked return towards the previous level of acuity after control of the diabetes. The author feels that the presence of ketosis demands insulin treatment and that the absence of ketosis is an indication that insulin is not required.—E. L.

True sugar control of skin and of muscle in diabetic and non-diabetic persons. Trimble, H. C. and B. W. Carey, J. Biol. Chem. **90:** 655. 1931.

In a series of observations upon non-diabetic hospital patients the true sugar content (fermentable reducing substance) of muscle, skin and blood averaged respectively 28, 56 and 110 mgm.%, while with a group of diabetic individuals the corresponding values were 51, 144 and 226 mgm.%. The true sugar content of muscles from diabetics who had received insulin shortly before the excision of the tissue averaged almost the same as that in a group which had not received insulin for at least 17 hours previously.

—H. C. Trimble.

The percentage of eosinophils in blood smears from insulin-treated diabetics. Watson, E. M., Am. J. M. Sc. **182:** 231. 1931.

The group examined consisted of 43 diabetics who had been receiving insulin 1 to 4 times a day for periods up to 6 years. In only one case was there a definite eosinophilia. The average percentage of eosinophils in the diabetics treated with insulin was not different from the group of 22 diabetics who were treated by diet alone.—E. L.

The respiratory quotient. Its use in the diagnosis of diabetes mellitus. Wishnofsky, M. and C. Byron, Arch. Int. Med. **48:** 470. 1931.

The disturbance in the metabolism of carbohydrates may be considered from three standpoints: the determination of the presence of glycosuria, changes in the concentration of sugar in the blood, and changes in the respiratory quotient. The renal threshold for dextrose varies from 45 to 348 mgm. per hundred cubic centimeters of blood. Glycosuria occurs in persons with a low renal threshold who are not diabetic. A diabetic person with a high threshold may have transient glycosuria or none. A high level of sugar in the blood during fasting, and especially a high blood sugar curve after the ingestion of dextrose, may occur in conditions other than diabetes, such as hypertension, nephritis and hyperthyroidism. From the scientific standpoint, the presence of glycosuria and hyperglycemia is inadequate for the diagnosis of diabetes mellitus. A respiratory quotient curve that rises to 0.88 after the ingestion of an adequate amount of dextrose is indicative of a normal secretion of insulin; a low respiratory quotient curve, with certain exceptions, indicates a diminution in the secretion of insulin, or a neutralization or inactivation of an adequate supply. In a study of both the blood sugar and the respiratory quotient curves after the ingestion of dextrose in two cases of hyperthyroidism and two of hypertension, it was demonstrated that the ultimate criterion in the diagnosis of diabetes mellitus is the respiratory quotient curve.—Authors' Summary.

Hereditary and familial diabetes mellitus. Wright, I. S., Am. J. M. Sc. **182:** 484. 1931.

A tendency to high blood sugar can be transmitted according to the law of Mendel in mice and other animals. It is suggested that the disease diabetes mellitus can be transmitted according to the same laws in human beings. All cases of diabetes are probably not hereditary, but careful questioning will increase the incidence of this occurrence in the records of a series of cases. Certain cases are presented to illustrate and emphasize the hereditary and familial factor of diabetes in the human race.—Author's Summary.

Spontaneous insulin resistance in rabbits: The effect of thyroidectomy on the response to insulin. Zeckwer, I. T., Am. J. M. Sc. **182**: 153. 1931.

Two rabbits were encountered that showed spontaneous resistance to insulin. One required 20 units for the development of convulsions, the other required 76 units. With subconvulsive doses the blood sugar remained for many hours near the convulsive level, but apparently release of glycogen from the liver, which is generally conceded to be due to activity of the sympathetic nervous system in which the adrenals are concerned, was more active in these rabbits than in normal ones, and in consequence sufficient glycogenolysis occurred to avert convulsions. Twenty-nine days fter thyroidectomy 2 units were sufficient to cause convulsions in the rabbit that previously had required 20 units; 17 days after thyroidectomy 5 units were sufficient in the rabbit that had previously required 76 units. Thyroidectomy, therefore, increased the response to insulin roughly 10 and 15 times, while, according to Burn and Marks, normal rabbits show an increase in response to insulin after thyroidectomy of 6 and possibly 9 times, and so far as our experiments have progressed Burn and Marks' figures have not been exceeded in the normal rabbit. The thyroid, therefore, seems to be one factor in this phenomenon of spontaneous insulin resistance, and these results tend to support the view that the thyroid influences the sensitiveness of the response of the sympathetic nervous system. However, these resistant rabbits after thyroidectomy still did not respond to the very small doses of insulin to which a normal rabbit responds after thyroidectomy, so that there must be other factors than the thyroid concerned in this insulin resistance.—Author's Abst.

Does the exocrine activity of the pancreas influence the secretion of insulin (L'activité exocrine du pancréas influe-t-elle sur l'insulino-sécrétion)? Zunz, E. and J. La Barre, Compt. rend. Soc. de biol. **104**: 790. 1930. Abst., Rev. belge sc. med. **3**: 101.

The object of this work was to find out if the flow of pancreatic juice produced by the introduction of hydrochloric acid into the duodenum is accompanied by a modification of the insulin secretion. Five to 10 minues after the introduction of acid into the duodenum of chloralosed adrenalectomized dogs there was a marked fall of blood sugar. The degree of hypoglycemia was to a certain extent in agreement with the quantity of pancreatic juice secreted. By the method of anastomosis of the pancreatic-jugular veins of decapsulated, chloralosed dogs there was produced a lowering of the blood sugar in the recipient dog which received the pancreatic venous blood of a donor secreting an abundant quantity of pancreatic juice following the injection of insulin. Such secretion persisted after sub-cardiac section of both pneumogastrics.

—J. Gagnon.

Hyperparathyroidism with hypercalcaemia and decalcification of bones. Hurst, A. F. and C. F. Cosin, Proc. Roy. Soc. Med. **24**: 707. 1931. (Sect. Med.)

The patient was a boy, aged 17, from whom a cystic parathyroid adenoma had been excised.—I. B.

Studies on the condition of phosphorous in parathyroidectomized and thyroparathyroidectomized animals (Recherches sur la phosphathémie des animaux parathyréoprives ou thyroparathyroidectomisés). Parhon, C. I. and G. Wener, Compt. rend. Soc. de biol. **104**: 228. 1930.

Two dogs were parathyroidectomized and nine thyroparathyroidectomized. The latter showed in the blood an increase of both mineral and organic as well as the total phosphorous. The ether extractable phosphorous is diminished and the lipoidal type little changed.—J. C. D.

Hyperparathyroidism with osteitis fibrosa cystica (parathyroid hyperplasia). Schnabel, T. G., Clin. North America, **14**: 977. 1931.

The patient described was a man of 26 who presented a blood calcium of 14 to 15.8 mgm. per 100 cc. of blood. The phosphorus content was 2.7 to 4.2 mgm. per 100 cc. X-rays revealed marked decalcification of all the bones of the body with innumerable fractures. The bones generally showed a more or

less cystic appearance and in some areas definite evidences of giant-cell tumors. There were also evidences of renal calculi. A mass in the left side of the neck, suspected of being parathyroid tissue, was removed and found to consist of hyperplastic parathyroid tissue. Soon after operation there was a drop in the calcium level to 11.5 mgm., but it has gradually returned to 13.8 mgm. The probabilities are that not all of the hyperplastic tissue or perhaps not all of the adenoma was removed. Here was a patient with widespread bone lesions which had predisposed him to multiple pathologic fractures. The clinical picture was that of generalized osteitis fibrosa cystica or Von Recklinghausen's disease. In such cases the long bones are the seat of cysts and tumors and show a lack of mineralization by x-ray examination. The swellings of the bones are often of a hemorrhagic-cystic nature, there is much fibrosis present and between the fibers one finds many giant cells. These tumors are probably benign, but are only distinguishable with difficulty from giant cell sarcoma. In this patient, presumably, there was a hyperactivity on the part of the parathyroids with a resulting hypercalcemia. In order to maintain the high blood calcium level, the bones had been robbed of their calcium. Under such circumstances the bones break easily and hemorrhagic cysts and giant-cell tumor formation result. Whether these cysts and tumors are secondary to the fractures or occur as primary lesions is uncertain. It is likewise undetermined whether the parathyroid dysfunction or lesion is primary or secondary to the bone lesions. There is a possibility that the parathyroid disturbance is a secondary one and that it is a compensatory response to a disturbed calcium metabolism due to some other cause. In fibrosa cystica, clinical and experimental evidence makes it seem probable that the parathyroid relationship to this disease is one of cause and effect. In any event, parathyroid surgery seems logical.—I. B.

Experimental chronic hyperparathyroidism: Metabolic studies in man. Wilder, R. M. and J. L. Johnson, Proc. Assoc. Am. Physicians. Abst., J. A. M. A. **96**: 1987. 1931.

Experiments of J. L. Johnson confirm work recently reported by Jaffé and Bodansky and reveal that the skeletal lesion produced in animals (rats and puppies) by chronic injections of parathyroid extract is a lacunar resorption of bone, accompanied by replacement of both marrow and cortical structures by fibrous connective tissue, the process including cyst formation and the accumulation of giant cells. The histologic picture is essentially identical to the generalized osteitis fibrosa that is found associated clinically with tumors of the parathyroid glands. The simultaneous injection of viosterol did not significantly influence the results. Calcium and phosphorus balance studies on two human subjects were included as a part of this study. The protocols of one of these were reported. Parathyroid extract, in a dosage of 50 units daily, caused an elevation of the calcium and depression of the phosphorus of the serum and a prompt increase in urinary excretion of both calcium and phosphorus, a moderate anemia and general weakness and pains in bones and joints. Giving viosterol with parathyroid extract did not significantly alter these effects. It was concluded that the pathogenesis of generalized osteitis fibrosa is clearly an oversupply of parathyroid hormone.

Influence of pregnancy on the thymus (Influence de la gestation sur le thymus). Jolly, J. and C. Lieure, Compt. rend. Soc. de biol. **104**: 451. 1930.

In young guinea pigs pregnancy is accompanied by an involution of the thymus. This involution is not permanent, for three weeks after delivery the gland has returned to a condition comparable to that of the control animals. —J. C. D.

The action of thymophysin on the human pregnant uterus in situ. Rucker, M., Am. J. Obst. & Gynec. **20**: 791. 1930.

It is extremely important that the obstetrician know the action of an oxytocic upon the human pregnant uterus in situ before he makes practical use of such a drug. Opportunity was taken to study the effect of thymophysin in four cases in which labor was induced with Voorhees bag, by connecting the stem of the Voorhees bag with a mercury manometer. The distal arm of the manometer was fitted with a float carrying an ink pen. In the first case, a II-para at term, ½ cc. of thymophysin showed no effect whatever. In cases 2, 3 and 4, the intramuscular injection of 1 cc. of thymophysin caused contrac-

tions of the uterus similar to those produced by posterior pituitary extracts, i.e., increased frequency of contractions without complete relaxation between "pains." The tendency to tetanus was more marked in the cases at term than in the case in which labor was induced at the 5th month.—Author's Abst.

Blood pressure and goiter. Askey, J. M. and C. G. Toland, California & West. Med. **34**: 80. 1931.

This paper is based upon the study of 550 case records. Regardless of age a systolic blood pressure of above 150 and a diastolic of above 110 is regarded as high, while a systolic below 110 is regarded as low. Of the patients observed 90% were women. Thirty and six-tenths per cent had hypertension; 2% had elevation of blood pressure above the normal for their age but not above 150. Five and four-tenths per cent had low blood pressure. The percentage of hypertension was slightly higher in the toxic adenoma than in the exophthalmic goiters. The basal metabolic rate of this group, consisting both of hyperthyroidism with adenoma and with hyperplastic thyroid was plus 33%. In the exophthalmic goiter patients with hypertension the pulse pressure increased more than in the adenomatous patients. Individually there was no definite correlation between the height of the B.M.R. and the height of the pulse pressure. In other regards, comparison of 100 records of toxic goiter with hypertension with another with normal pressure showed a greater tendency of toxic adenoma toward hypertension. The greater the duration of thyrotoxicosis the more likely hypertension will develop.—I. B.

Hyperthyroidism. Gallant, I. W. (for Patterson, D.), Proc. Roy. Soc. Med. **24**: 569. 1931. (Sect. Study Dis. in Child.)

The patient described was a child of 10 years 1 month old who presented the typical clinical features of exophthalmic goiter. The very interesting feature in this case is the fact that the condition had been active for the past 8 years. Indeed, a photograph taken of the patient at the age of 4 months revealed marked exophthalmos.—I. B.

The mechanism of colloid release from the urodele thyroid during diagnostic stages of metamorphosis (Amblystoma jeffersonianum, Amblystoma opacum). Grant, Madeleine P., Anat. Rec. **51**: (No. 1). 1931.

From a study of the thyroids of 18 Amblystoma jeffersonianum and 29 Amblystoma opacum during diagnostic stages of metamorphosis the process of colloid release through the cytoplasm of the follicular cells was observed. Glands were studied three and four days after the shedding of the initial molt, and during this time no evidence of refilling and return of the gland to the normal could be observed. Reduction of the follicular colloid, although considerable, was never so complete as that obtained experimentally, and therefore the intracellular material was never so abundant. The release of colloid during metamorphosis showed the same cytological patterns as seen in the experimental series and likewise gave evidence of transcellular export of stored colloid. The process occurred so much more slowly and was never so complete, so that, without the exaggerated pictures of the experimental studies, interpretation would have been less convincing. From an analysis of accumulated data the following hypothesis of the thyroid cycle is suggested. The chromophobic and chromophilic material are different phases of the secretory product. The intracellular presence of both are patterns which characterize the follicle in the process of colloid release. The identical pattern is seen in thyroid recovery when the follicle is in a process of refilling.—Author's Abst.

Iodine deficiency and goiter; influence of a diet poor in iodine on the thyroid gland in white rats. Hellwig, C., Arch. Path. **11**: 709. 1931.

Chatin's theory that endemic goiter is the result of a deficiency of iodine is accepted by most American scientists. A direct experimental proof for this assumption has never been attempted in this country. In Southern Germany, Tanabe succeeded in producing hyperplasia of the thyroid gland by giving white rats a diet poor in iodine. This locality being situated, however, in a goiter district, Tanabe's positive results cannot be regarded as conclusive. Hellwig therefore repeated Tanabe's experiments in Wichita, Kansas, where

endemic goiter is unknown. Neither Tanabe's iodine poor diet nor a much more severe, iodine-free diet was effective in producing hyperplasia of the thyroid gland. The author was led to the conclusion that the essential cause of goiter is a positive agent. He was able to produce marked hyperplasia of the thyroid gland in white rats by giving drinking water which contained 2% of calcium chlorid. The experimental goiter was parenchymatous, when the diet was iodine poor, while the produced goiters were of the colloid variety, when the diet was iodine rich. It is concluded from these experiments that an insufficiency of iodine is not the essential cause of goiter, but that a positive world-wide agent—for instance, excess of calcium—is responsible for the development of goiter. The anatomical structure of goiter seems, however, to depend on the iodine content of the food.—Author's Abst.

The cardiovascular system in goiter. Hurxthal, L. M. and O. J. Menard, West. J. Surg. (October, 1930). Read before the American Association for Study of Goiter, July 11, 1930.

An analysis of 100 cases personally studied led the authors to conclude that the clinical entity known as thyroid heart disease is as yet unproved. Cardiac enlargement is no more frequent in toxic goiter than in non-toxic goiter. Patients relieved of hyperthyroidism show no definite evidence of having higher blood pressure than other individuals. Arteriosclerosis as determined by the finding of calcified aortic placques is no more frequent in toxic than non-toxic goiter. Rheumatic heart disease is fairly frequent in toxic goiter in New England. Other cardiovascular disease plays a minor but at times important part in hyperthyroidism.—R. G. H.

Creatinuria in hyperthyroidism. Kepler, E. J. and W. M. Boothby, Am. J. M. Sc. **182**: 476. 1931.

In a series of 145 cases of hyperthyroidism composed of 115 cases of exophthalmic goiter and 30 cases of adenomatous goiter with hyperthyroidism, creatinuria occurred in 89 cases (61%). The incidence of creatinuria in exophthalmic goiter was 61% and in adenomatous goiter with hyperthyroidism 63%. Of 25 female patients with exophthalmic goiter not treated with iodin, creatin was found in the urine of 21 (84%); of 8 men similarly affected and not treated with iodin, creatinuria occurred in all 8. In a control group of 274 patients not having disease of the thyroid gland, creatin was found in marked or definite amounts in the urine of 14% of the women; in an additional 9% traces of creatin were found. Creatin in definite or marked amounts was not found in the urine of any of the men; in 9% of the men traces of creatin were found. Palmer's observation on the effect of the administration of iodin in reducing the amount of creatin excreted by patients with exophthalmic goiter was confirmed. However, the assumption that the reduction of creatinuria is a specific effect of iodin is not justified, as it is equally as logical to assume that the diminished excretion of creatin occurs as a result of the improvement in the general health of patients with exophthalmic goiter which follows the administration of iodin. For a few days immediately after thyroidectomy the excretion of creatin in exophthalmic goiter may increase in amount or occur when it has been previously absent, even though the administration of iodin is continued.—Authors' Summary.

Iodin in exophthalmic goiter. A comparison of the effect of ethyl iodid and potassium iodid with that of Lugol's solution. Lerman, J. and J. H. Means, Am. J. M. Sc. **181**: 745. 1931.

After the basal metabolism had reached a level on rest alone, iodin or iodids were administered. Ethyl iodid was administered by means of inhalation. In 5 of the 25 cases, 2 gm. were given daily and the remainder received 4 gm. each day. These inhalations were continued until the metabolism again reached a level. Lugol's solution (2 cc.) was then substituted for the ethyl iodid for 3 days or more and followed by a subtotal thyroidectomy. In patients treated with potassium iodid, a similar procedure was followed. Three of the patients received 0.18 gm. daily and the remainder 0.36 gm. daily. The average daily fall of the basal metabolic rate in patients receiving ethyl iodid was 3.7%, with potassium iodid, 4.5% and with Lugol's solution, 4.1%. The other symptoms and signs of the thyrotoxic state showed the same changes

during the ethyl iodid and potassium iodid administration as would be expected from adequate doses of Lugol's solution. It is suggested that potassium iodid solution is preferable to Lugol's solution because it is equally effective and less disagreeable to take.—E. L.

Persistence of an accelerated rate in the isolated hearts and isolated auricles of thyrotoxic rabbits; response to iodides, thyroxine and epinephrine. Lewis, J. K. and D. McEachern, Bull. Johns Hopkins Hosp. **48**: 228. 1931.

Normal rabbits were given thyroid extract by mouth or thyroxine subcutaneously for periods of from two to eighty-one days. At the end of this time the hearts were removed and perfused with Ringer-Locke solution or the auricles dissected free and suspended in a Dale bath filled with Ringer-Locke solution. Both the isolated hearts and auricles were found to continue to beat at a rate 26 to 54% faster than similar preparations from normal animals. Iodine and iodides in concentrations of 1:100,000 to 1:4,000,000 had no effect on the isolated auricle but caused moderate decreases in rate in 5 of 11 and in amplitude of contraction in 8 of 11 isolated hearts. There was no difference in the response of preparations from normal and thyroid treated animals. Thyroxine and desiodothyroxin had no immediate effect on normal or thyroid treated animals. The per cent increase in rate and amplitude of contraction after epinephrine was the same in normal and thyroid treated animals.

—J. K. Lewis.

The coexistence of myxedema and pernicious anemia. Means, J. H., J. Lerman and W. B. Castle, Tr. A. Am. Physicians, **45**: 363. 1930.

This paper is illustrated with five case histories. Myxedema may resemble pernicious anemia and vice versa. Also, the two diseases may coexist. Under such circumstances each disease responds to its appropriate treatment. Knowledge that the two may coexist is important to the clinician for it seems certain that some patients require treatment with both liver and thyroid.—I. B.

Influence of thyroid and thymus on skeleton formation in Italian partridges (Der Einfluss der Schilddruese und des Thymus auf die Skelettbildung bei Rebhuhnfarbigen Itailenerhuehnern). Nevalonnyj, M. and J. Podhradsky, Vestnik. Bull. Czechoslov. Acad. Agric. **6**. 1930.

Bone measurements, length and width, were made on the birds used for the above reported experiment. Thyroid, per os, caused some smaller extremity bones to remain shorter and somewhat wider than normal, while the larger bones showed the opposite tendency. Thymus retarded length growth and increased the thickness of all bones, much more so than thyroid. Only a small number of birds were used.—F. Gudernatsch.

Native complement in hyperthyroidism. Novick, N., Arch. Int. Med. **48**: 462. 1931.

This study was undertaken to ascertain the possibility of using the native complement value in the serum of patients with hyperthyroidism as a supplementary test in the diagnosis of hyperthyroidism. It was hoped that the adoption of such a laboratory procedure would rest on the determination of an increase in the complement titer of persons with hyperthyroidism and on its relation to the basal metabolic rate. In all, 110 controls were used, in 30 of whom the basal metabolic rate was normal, and in 80 of whom the basal metabolic rate was not suspected to have been abnormal. The complement titer in normal controls, in the determination of which an antisheep rabbit hemolytic serum, a 2.5% sensitized sheep cell suspension and incubation in the water bath at 37.5 C. for fifteen minutes were employed, was found to be 0.02 cc. of active serum in about 50% of the cases. A titer of 0.01 is next in frequency in about 35% of the cases. A high complement titer as well as a very low titer is infrequent. No increase of complement value or significant deviation from the average normal range was found in a group of 31 unclassified cases of hyperthyroidism. A high titer (0.005) was found in three cases or 10%, in two of which the basal metabolic rate was also high, which appears to be a mere coincidence. The postoperative and preoperative complement value in the serum of patients with hyperthyroidism when compared with the postoperative and preoperative basal metabolic rates does not suggest any signifi-

cant relationship. No change in titer was noted in 55% of the cases, while a higher complement value was obtained in 36% of the cases following thyroidectomy.—Author's Summary.

The resorption of physiologic solution injected intradermally and subcutaneously in a myxodematous idiot. Relation between the thyroid and tissue fluid (Sur la résorption de la solution physiologique injectée par voie intradermique ou sous-cutanée dans un cas d'idiote myxoedémateuse. Rapports du corps thyroide et de l'hydrophilie tissulaire). Parhon, C. I. and L. Mavromati, Compt. rend. Soc. de biol. **104**: 220. 1930.

Solutions were injected intradermally and subdermally in the idiot and in a control. In both situations absorption of the fluid was slower in the case of myxodema.—J. C. D.

Incidence of exophthalmic goiter in Olmstead County, Minn. Plummer, H. S., Proc. Am. Assoc. Physicians. Abst., J. A. M. A. **96**: 1988.

The incidence of exophthalmic goiter in the United States is not known. Prevailing thought regarding the relative incidence in different sections of the country is to a high degree inferential. That it is relatively high in the upper Mississippi Valley and Great Lakes region has been recognized for many years. The author is confident that the number of cases in the Northwestern states has progressively and periodically increased during the last fifty years. It is probable that a wave of higher incidence followed the influenza epidemics of 1899 and 1918. The latter wave was marked by high intensity and mortality. Data indicate a low incidence in 1923. Correlation of a number of observations led to the conclusion that the incidence of exophthalmic goiter and adenomatous goiter with hyperthyroidism rapidly increased in 1924, reached its height in 1926 and 1927, gradually diminshed in 1928 and 1929, and dropped rapidly to the 1923 level in 1931. At the height of this wave the incidence was accompanied by a marked increase in intensity of adenomatous goiter with hyperthyroidism. Without any implications regarding etiology, the author will for convenience refer to this wave of high incidence as an epidemic. There has occurred a definite drop in the incidence of adenomatous goiter with hyperthyroidism, as indicated by basal metabolic rate studies. That there has been a corresponding drop in the intensity of exophthalmic goiter seems probable, but the evidence is too confused by the use of iodine in the treatment to permit as yet a definite opinion. The observations that first suggested the probability of this epidemic were too sudden a change in the number of patients having exophthalmic goiter and adenomatous goiter, coming to the Mayo Clinic from certain sections, to be reasonably accounted for except by a change in incidence, a coincident change in sex ratio, a marked change in the proportion of cases of adenomatous goiter with and without hyperthyroidism, and the sharp elevation of average basal metabolism in patients having adenomatous goiter with hyperthyroidism. As there was no direct way of ascertaining the percentage of hyperthyroid patients in the Northwest and the Great Lakes region, the conclusion that an epidemic had occurred is to a degree inferential. The analysis of the data on which the conclusion is reached is involved, difficult to present, and too incomplete to report, except for a study of Olmstead County and three adjacent counties in Southern Minnesota. In this territory, for twenty years at least, thyroidectomy has been almost universally accepted as a standard way of treating exophthalmic goiter and adenomatous goiter with hyperthyroidism. The diagnosis of adenomatous goiter with hyperthyroidism has not sufficiently changed to affect the material to be presented. Since the introduction of basal metabolic rate estimations in 1917, the total number has been slightly increased by the addition of a few mild cases. On the assumption that only half of the patients were operated on before 1917, and the majority after 1917, the curves of incidence are not materially changed so far as demonstrating the occurrence of an epidemic after 1923. There is not sufficient evidence to justify an opinion regarding the cause of this epidemic. The report is made at this time to elicit interest in the study of the problem by men throughout the country. The onset of the epidemic was almost, if not actually, coincident with the introduction of iodized salt. At the present time, both the incidence and the intensity are low. The use of iodized salt has increased since the onset of the epidemic. The evidence does not at present warrant an attack on the use of iodized salt. A limited amount of data indicates a low incidence in Michigan. The use of iodine in the treatment did not cause the high incidence of exophthalmic goiter.

Influence of thyroid and thymus on growth of castrated and non-castrated Italian partridge-cocks (Der Einfluss der Thyreoidea und des Thymus auf das Wachstum Kastrierter und Nichtkastrierter Rebuhuhnfarbiger Italienerhaehne). Podhradsky, J., Vestnik. Bull. Czechoslov. Acad. Agric. **6.** 1930.

It had been reported previously by Krizenecky and Nevalonnyj that hyperthyroidization of chicks caused a depression of the growth rate, more in males than in females, while hyperthymization of very young birds led to an acceleration, in older to a depression, of the growth rate which, however, was less than the depression caused by thyroid. These authors assumed a thyroid-thymus antagonism as far as growth was concerned. The present writer castrated 3-months-old cocks and fed thyroid, 0.1 g. per 100 body weight daily, and observed in this group (A) at first very slow growth, later acceleration and prolongation of growth. A second normal group (B) received 20 grams (?) of thyroid during 14 days, after that 0.1 g. (per 100 g.) thymus daily. This group showed slower growth of much less duration than A. A third normal group (C) received daily 0.1 grams of thyroid (per 100 g.) and the same amount of thymus. This group showed faster growth but of less duration than A. Thus, hyperthyroidization retards growth of castrated cocks less than of non-castrated. Sixteen experimental animals were used, and the experiment lasted 178 days.—F. Gudernatsch.

Investigations on the action of thyroxin in pregnancy (Untersuchungen über die Wirkung des Thyroxins in der Schwangerschaft). Siedentopf, H., Monatschr. f. Geburtsh. u. Gynäk. **85:** 325. 1930.

The author has investigated the influence of pure synthetic thyroxin on certain aspects of pregnancy. Experiments with guinea pigs showed a marked loss in weight of the mother who was delivered of normal but underweight young when heavy doses were administered. On this basis attempts were made to retard growth of the foetus in pregnant women with contracted pelves. In a series of 17 thus treated, the average foetal weight was some 6% below the usual clinic average, and the length over 3% less. The doses of thyroxin were small, however, as shown by the fact that the mothers showed normal weight increases during the period of treatment. The author concludes that this may be a therapeutic lead for the care of the patient with a narrow pelvis but urges extreme caution in practice. The use of thyroxin with pregnant women having apparently normal kidneys, but with edema, a condition ascribed by some to thyroid failure, had no effect upon the water metabolism. Likewise its use with preclamptic and overdue patients was without apparent influence on the time of onset of uterine contractions. An earlier paper had demonstrated that thyroxin injections in the mother was without influence on the foetal heart rate. In the present studies the newborn children gave no evidence of any thyrotoxicosis from the therapeutic programme.—A. W. R.

Respiration of the thyroid gland (Stroffwechsel studien an der überlebenden Schilddrüse. V. Die Gewebsatmung der Schilddrüse und ihre Beeinflussungsmöglichkeit durch Jod und Hormone). Sturm, A., Ztschr. f. d. ges exper. Med. **74:** 555. 1930. Abst., Physiol. Absts. **16:** 197.

Using Warburg's technique, it was found that dog's thyroid does not differ in O_2 utilization or fermentative power from other tissues. The thyroids of iodine-fed dogs show lower respiratory values and a somewhat greater power of fermentation. Thyroid and thyroxine feeding do not modify these findings. Colloid goiters had in 4 cases normal respiratory values and slightly increased anaerobic fermentation; six goiters from Graves' disease showed much greater fermentative powers than either normal glands or colloid goiters. Addition of small quantities of inorganic iodine caused a fall in the O_2 quotient and frequently an increase in anaerobic and aerobic glycolysis. Thyroxine, adrenaline, and insulin have no effect on the respiratory phenomena of dog's thyroid gland.

Studies in the etiology of simple goiter. Webster, B. and A. M. Chesney, Am. J. Pathol. **6:** 275. 1931.

Further investigations into the etiological factors involved in an epidemic of simple goiter in rabbits are reported. A diet which consists almost exclusively of cabbage appeared to be the major etiological factor. Fecal and uri-

nary contamination of food seemingly played no rôle in the epidemic. The addition of water (either tap or distilled) to the diet exerted no appreciable protective influence against the goitrogenic agent. Iodine, administered orally in quantities of 7.5 mgm. per week, will completely protect the animal against the goiter-producing factor. There is no evidence that the minute traces of iodine contained in Baltimore city tap water exert any detectable protective influence. The goitrogenic agent is much more active in winter than in the summer months. This goiter-producing factor appears to be a nutritional one and may act through the oxidation-reduction systems of the body.

—Authors' Summary.

Effect of experimental hyperthyroidism on reproductive processes of female albino rats. Weichert, K., Physiol. Zoöl. **3**: 461. 1930.

The solution of this problem was undertaken by feeding desiccated thyroid to pregnant and non-pregnant rats in definite amounts over various periods. Ten mature females were fed daily 0.25 g. of desiccated thyroid from the beginning of pregnancy, as determined by vaginal smears. Part resorbed their young, part died; half delivered young from one to four days overtime, all born dead or dying within one or two days. With 9 other animals the same procedure, except the amount fed, was 0.5 g. daily, resulted in similar but more pronounced effects. Twelve normal rats fed daily 0.25 g. went into dioestrous after about two cycles and so remained as long as fed, with but a single exception. All lost in weight. It is suggested that the continued condition of dioestrous was due to persistence of the corpora lutea brought about by the anterior pituitary under the influence of experimental hyperthyroidism, and also that delay in parturition was due to the lack of oestrous-producing hormone following the increased metabolism.—E. P. D.

Masked gastro-intestinal hyperthyroidism. Report of thirty-four cases. Verbrycke, J. R., Jr., J. A. M. A. **97**: 513. 1931. Abst., A. M. A.

The author states that, while the picture of a typical case of toxic thyroid has always been fairly clear, it is only during the past several years that he has appreciated the fact that the thyroid can play such an important part in the production of gastro-intestinal symptoms without giving the usual thyroid syndrome and without demonstrable enlargement of the gland. During the last three years the author has had 34 patients coming for gastro-intestinal diagnosis, the cause of whose symptoms was proved to be thyroid, in masked form, so that in many instances the thyroid was not suspected at first examination. Cases of frank toxic thyroid are not included in this series. When it is considered that these 34 cases were recognized in three years, after attention was focused on the condition, it is a cause of intense chagrin to realize how many diagnoses have been missed in the last twenty years. An analysis of the presenting symptoms or chief complains of the patients shows that "nervousness" occupied first place in 11 and general abdominal pain and cramps in 10; but if two cases presenting paid in the upper abdominal region; two, tight ache in the abdomen; one, misery in the stomach, and one, hunger pain, were grouped together as abdominal pain, the total would take first place with a count of 16. Nausea and vomiting occurred in 9; palpitation in 7; weakness in 7; gas in 5, and diarrhea in 3 cases. While only two patients complained of loss of weight as the symptom which caused them sufficient anxiety to make them seek relief, questioning showed that 24 had lost weight, varying from 2 to 40 pounds (0.9 to 18 kgm.), with an average for the entire series of 9.6 pounds (4.4 kgm.). On examination, rapid pulse was one of the first things to attract attention. The last of the important observations is tremor. Only two patients failed to show tremor at some time. It is interesting to note concomitant conditions found. Twenty of the 34 patients had anemia, 19 indicanuria, 10 ptosis and 9 vagotonia. The cause for the high proportion of anemias is not so easy to discover, but most of the other observations can be fitted into the proper place in the picture. Thus the vagotonia and irritable colon are what might be expected in the type of person with hyperthyroidism. It is not surprising that 10 should have the condition diagnosed as nerve exhaustion.